NUEVOS TRATAMIENTOS EN CANCER DE MAMA LUMINALES

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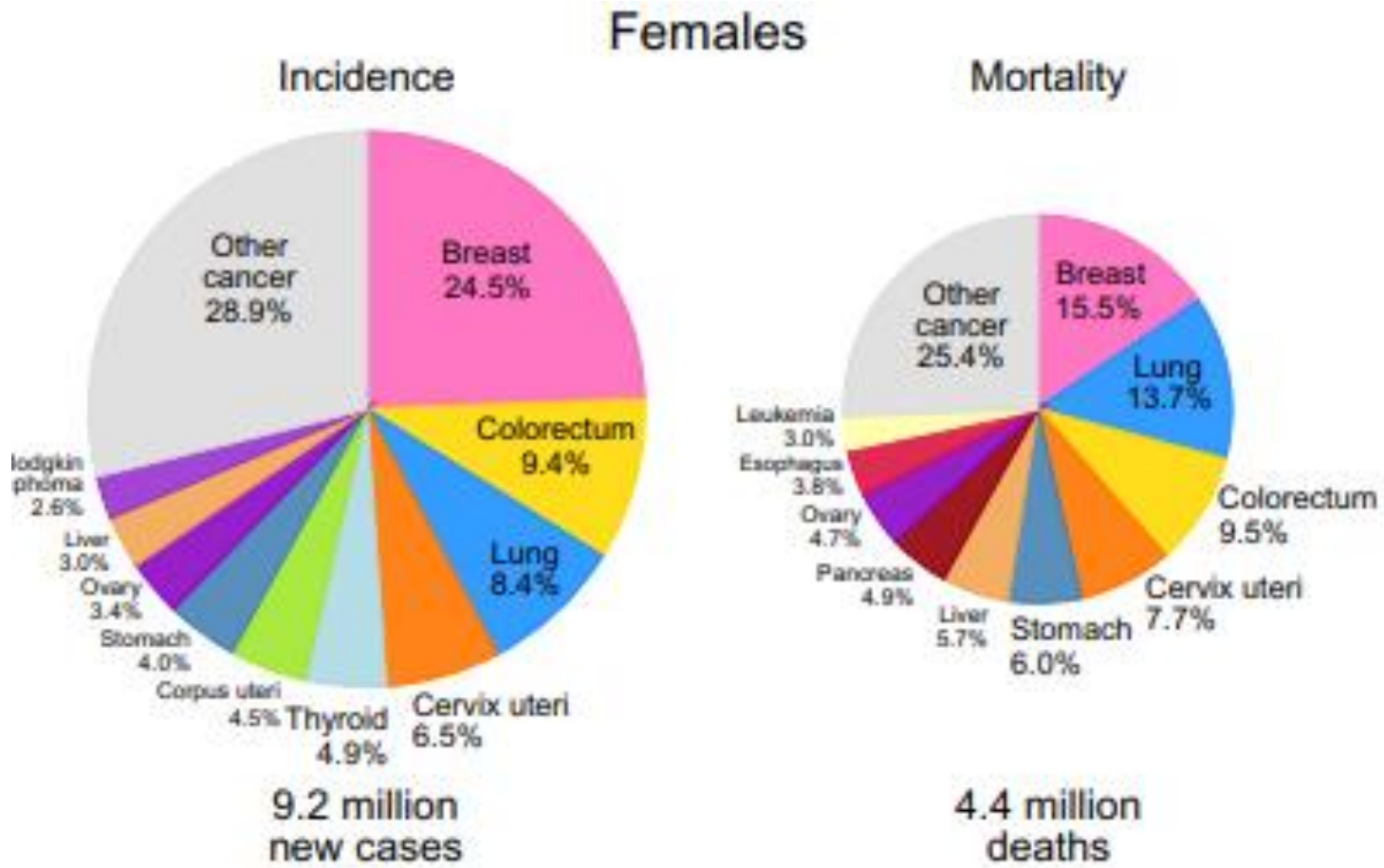


FIGURE 4. Distribution of Cases and Deaths for the Top 10 Most Common Cancers in 2020 for (A) Both Sexes, (B) Men, and (C) Women. For each sex, the area of the pie chart reflects the proportion of the total number of cases or deaths; nonmelanoma skin cancers (excluding basal cell carcinoma for incidence) are included in the "other" category. Source: GLOBOCAN 2020.

Necesidad no reunidas en Ca de mama RH+

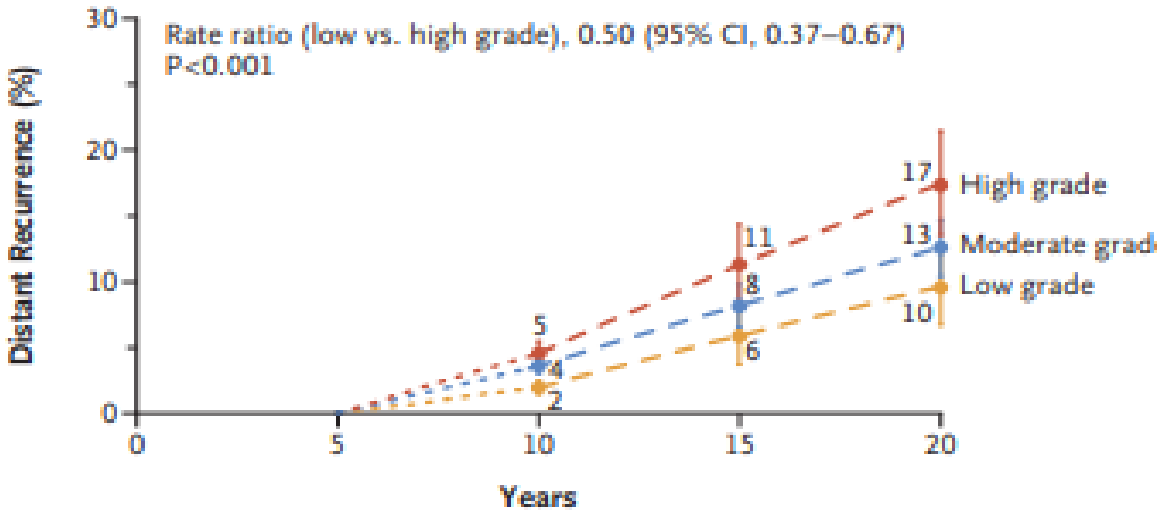
Enfermedad temprana

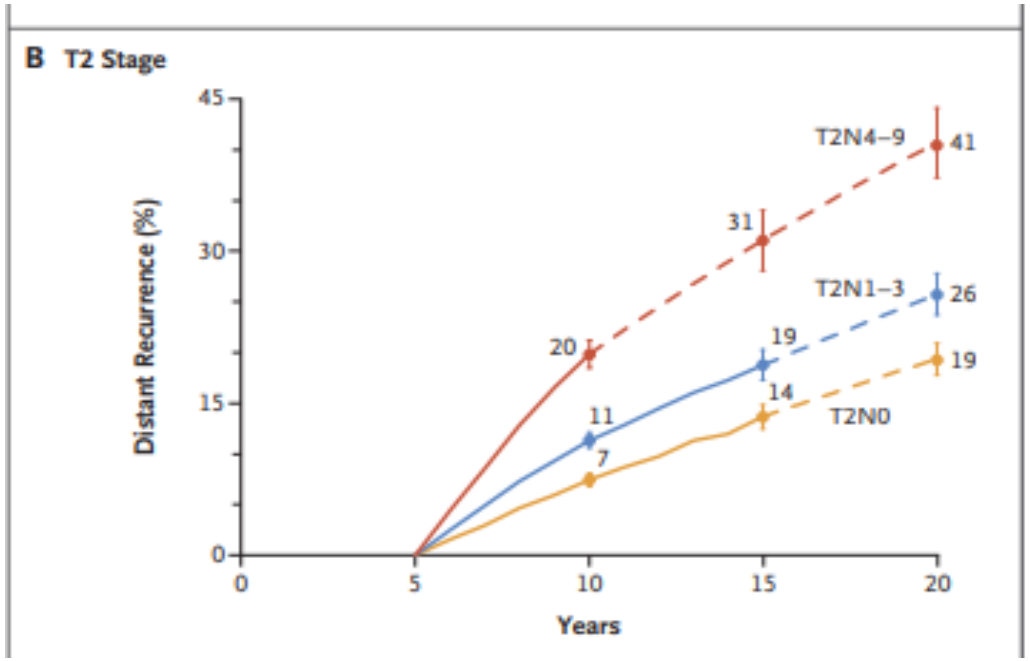
- Beneficio de TE, los pacientes aun tiene riesgo de desarrollar recurrencias
- Poder identificar a pacientes de alto riesgo de recurrencia, nos permite escalar la terapia en la adyuvancia

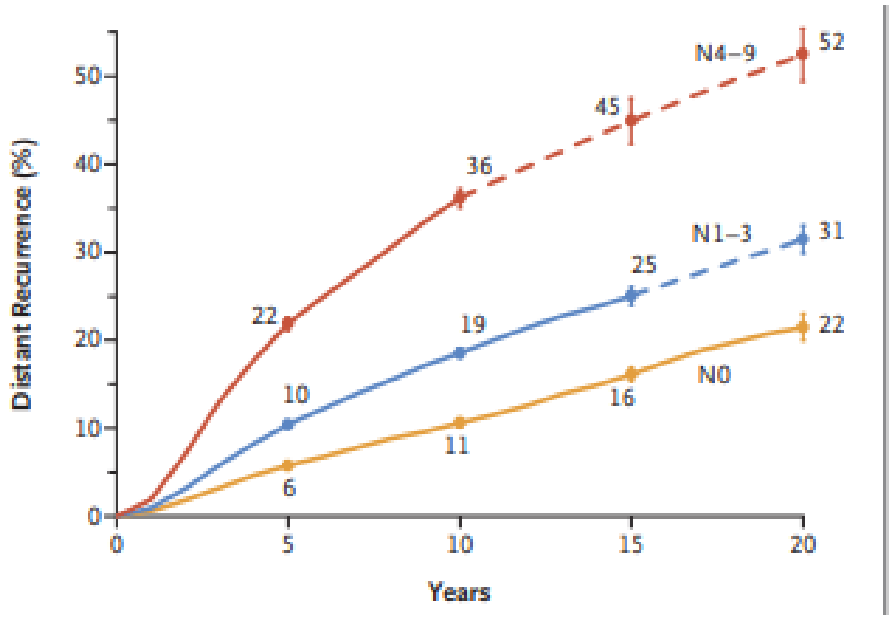
Enfermedad avanzada

- La eficacia de la TE disminuye con el tiempo
- Prolongar el tiempo hasta la aparición de la resistencia endocrina puede retrasar el inicio de la quimioterapia
- Manter la HRQoL es esencial

Riesgo Continuo de recurrencia

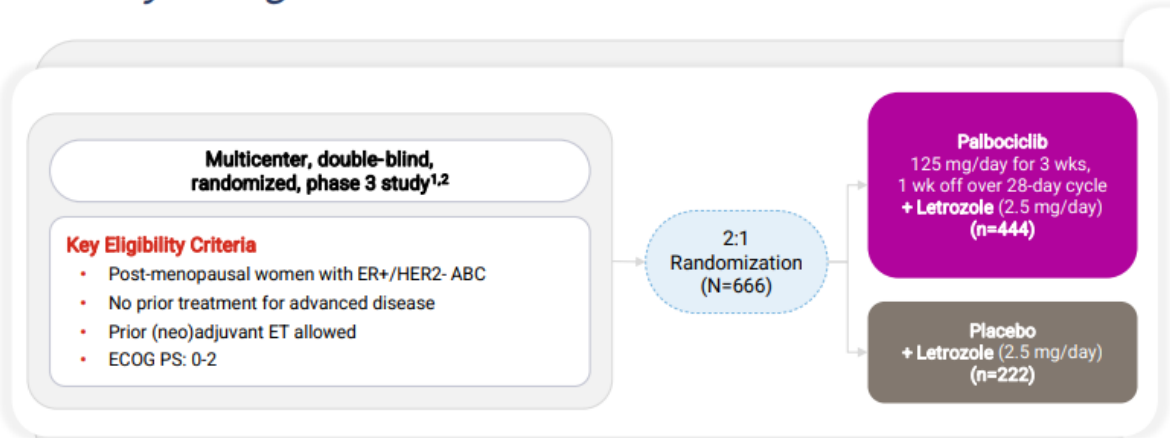




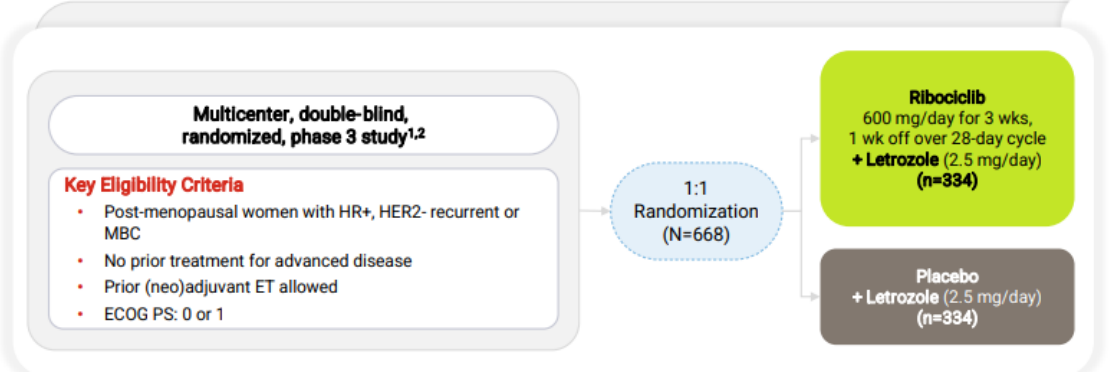


n engl j med 377;19 nejm.org November 9, 2017

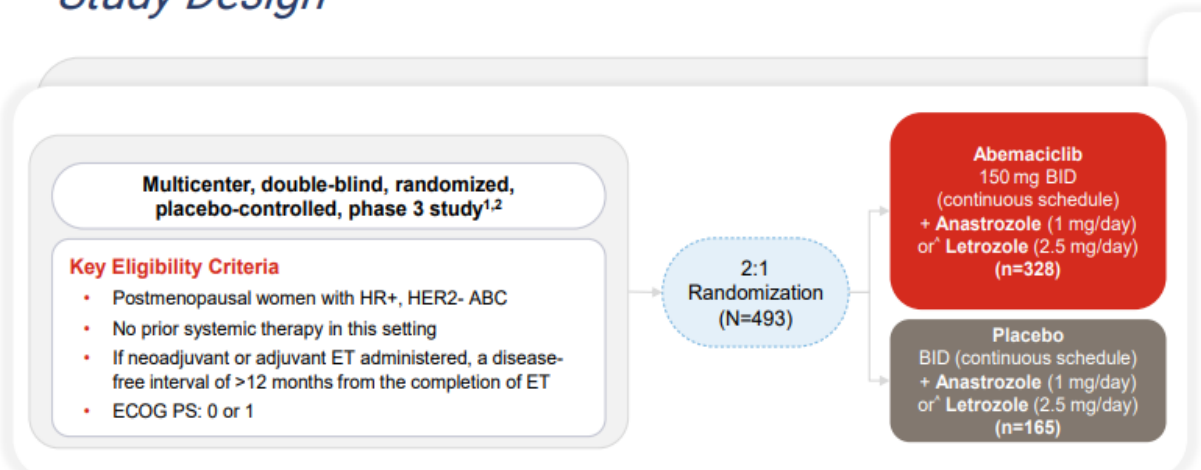
PALOMA-2
Study Design



MONALEESA-2
Study Design



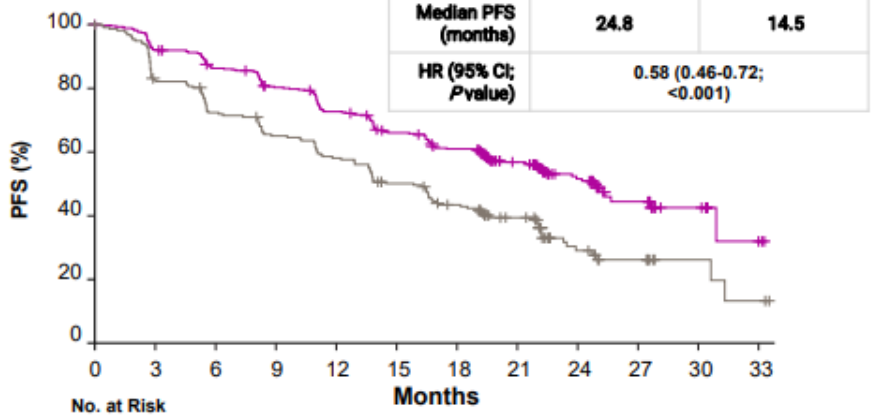
MONARCH 3
Study Design



PALOMA-2
Efficacy Results

Investigator-Assessed PFS[1a]

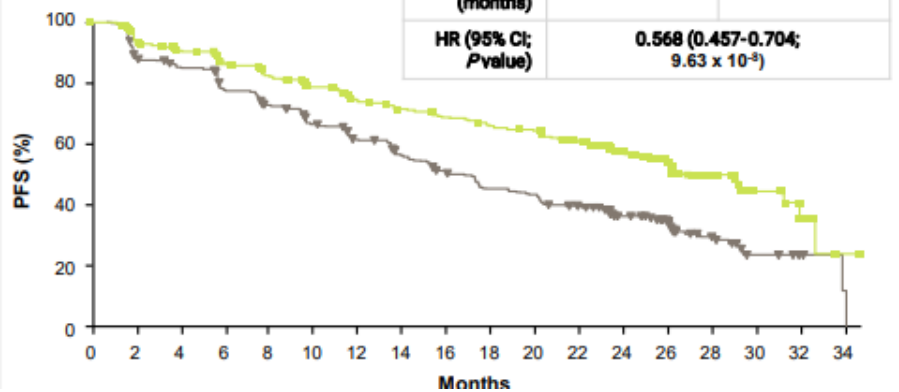
	Palbociclib + Letrozole	Placebo + Letrozole
Median PFS (months)	24.8	14.5
HR (95% CI; *P* value)	0.58 (0.46-0.72; <0.001)	



MONALEESA-2
Efficacy Results

Investigator-Assessed PFS[a] (Updated Analysis)[1]

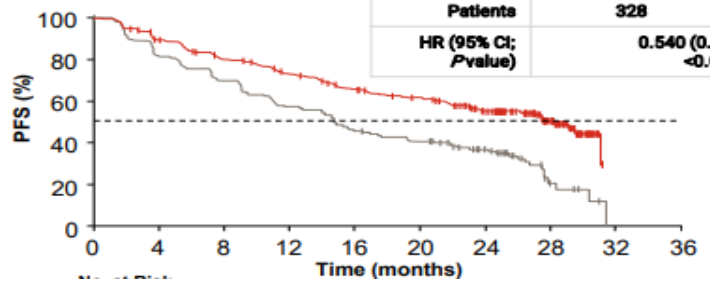
	Ribociclib + Letrozole	Placebo + Letrozole
Median PFS (months)	25.3	16.0
HR (95% CI; *P* value)	0.568 (0.457-0.704; 9.63×10^{-8})	



MONARCH 3
Efficacy Results – PFS in the ITT Population

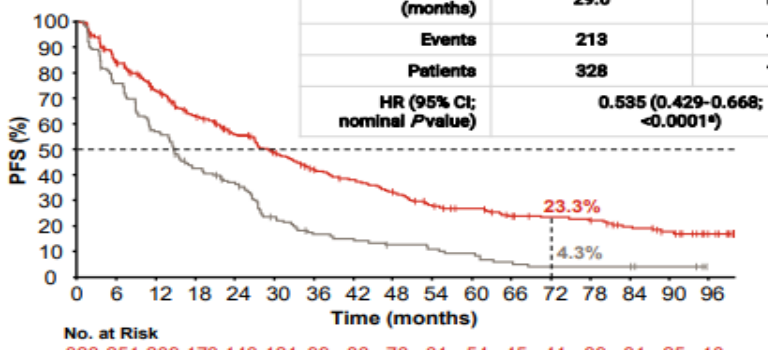
Investigator-Assessed Final PFS[1a]

	Abemaciclib + NSAI	Placebo + NSAI
Median PFS, (months)	28.2	14.8
Events	138	108
Patients	328	165
HR (95% CI; *P* value)	0.540 (0.418-0.698; <0.0001)	



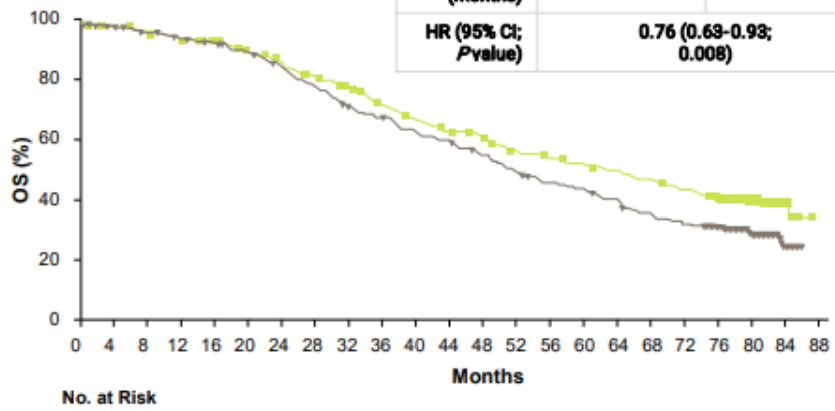
Updated PFS[2b]

	Abemaciclib + NSAI	Placebo + NSAI
Median PFS, (months)	29.0	14.8
Events	213	137
Patients	328	165
HR (95% CI; nominal *P* value)	0.535 (0.429-0.668; <0.0001[c])	



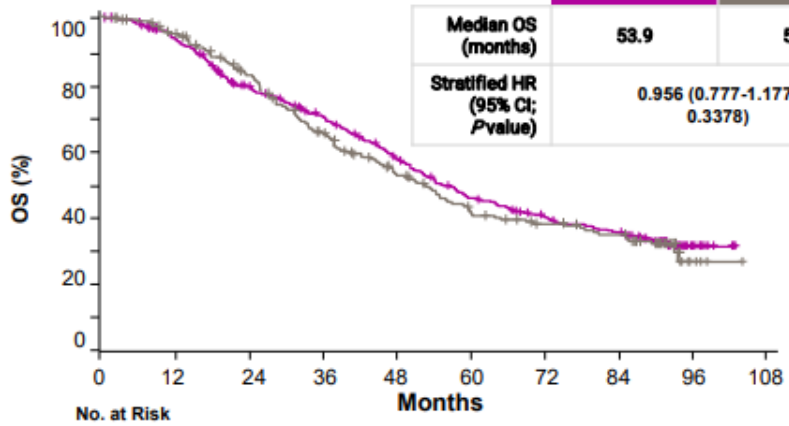
OS Benefit[2b]

	Ribociclib + Letrozole	Placebo + Letrozole
Median OS (months)	63.9	51.4
HR (95% CI; *P*value)	0.76 (0.63-0.93; 0.008)	



Final Overall Survival[2b]

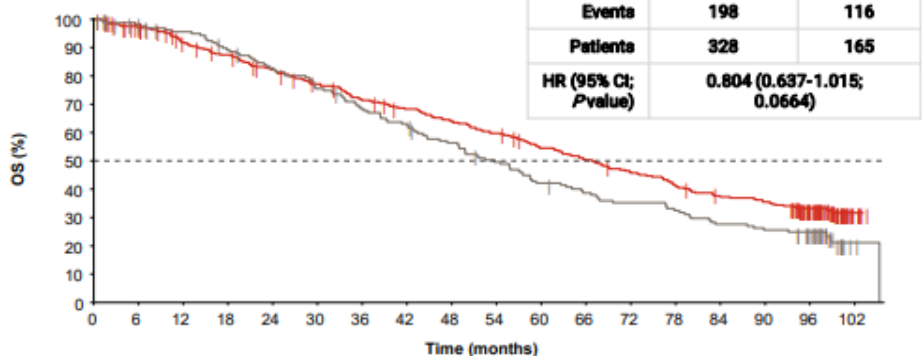
	Palbociclib + Letrozole	Placebo + Letrozole
Median OS (months)	53.9	51.2
Stratified HR (95% CI; *P*value)	0.956 (0.777-1.177; 0.3378)	



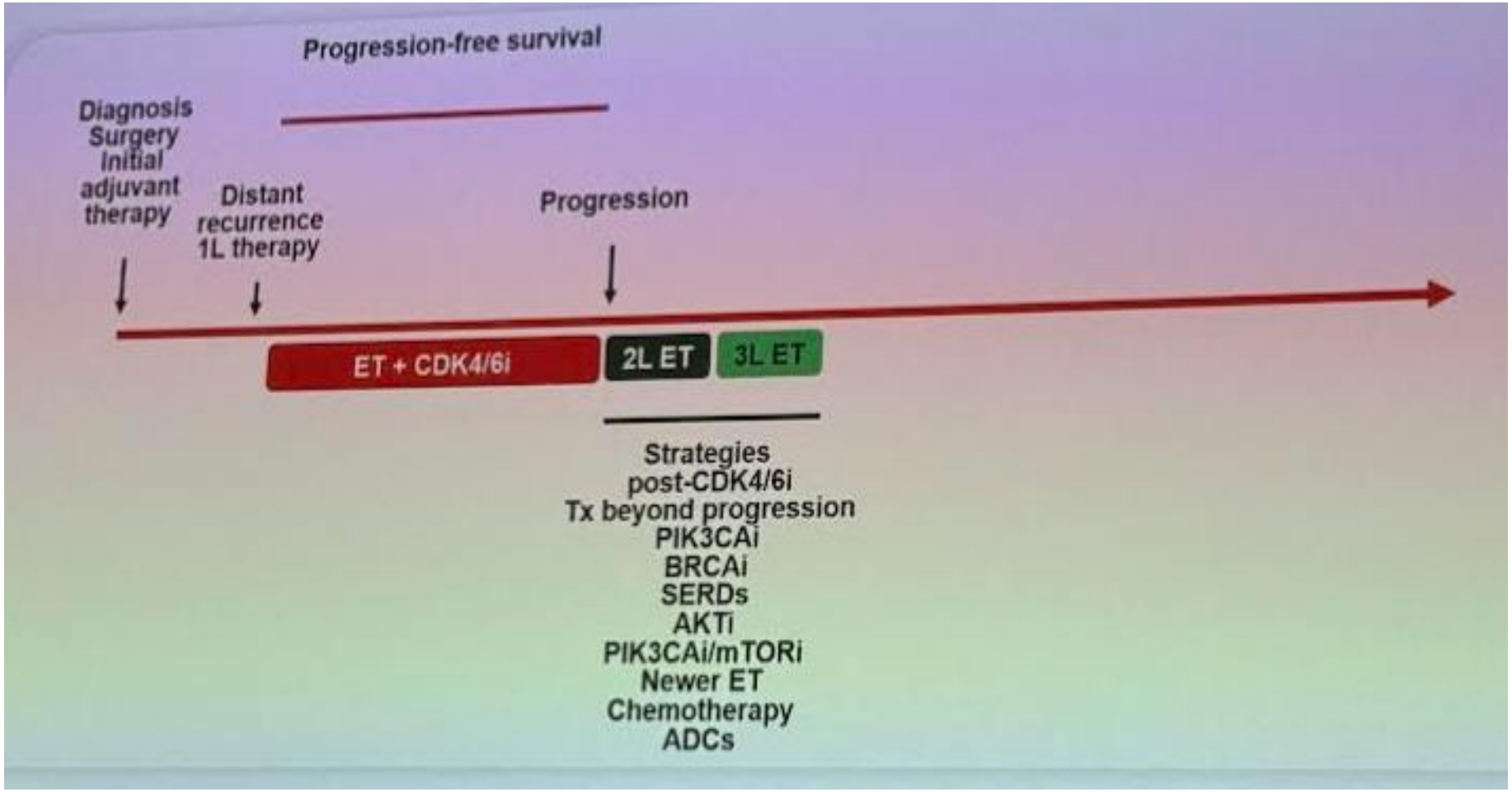
Efficacy Results – Overall Survival*

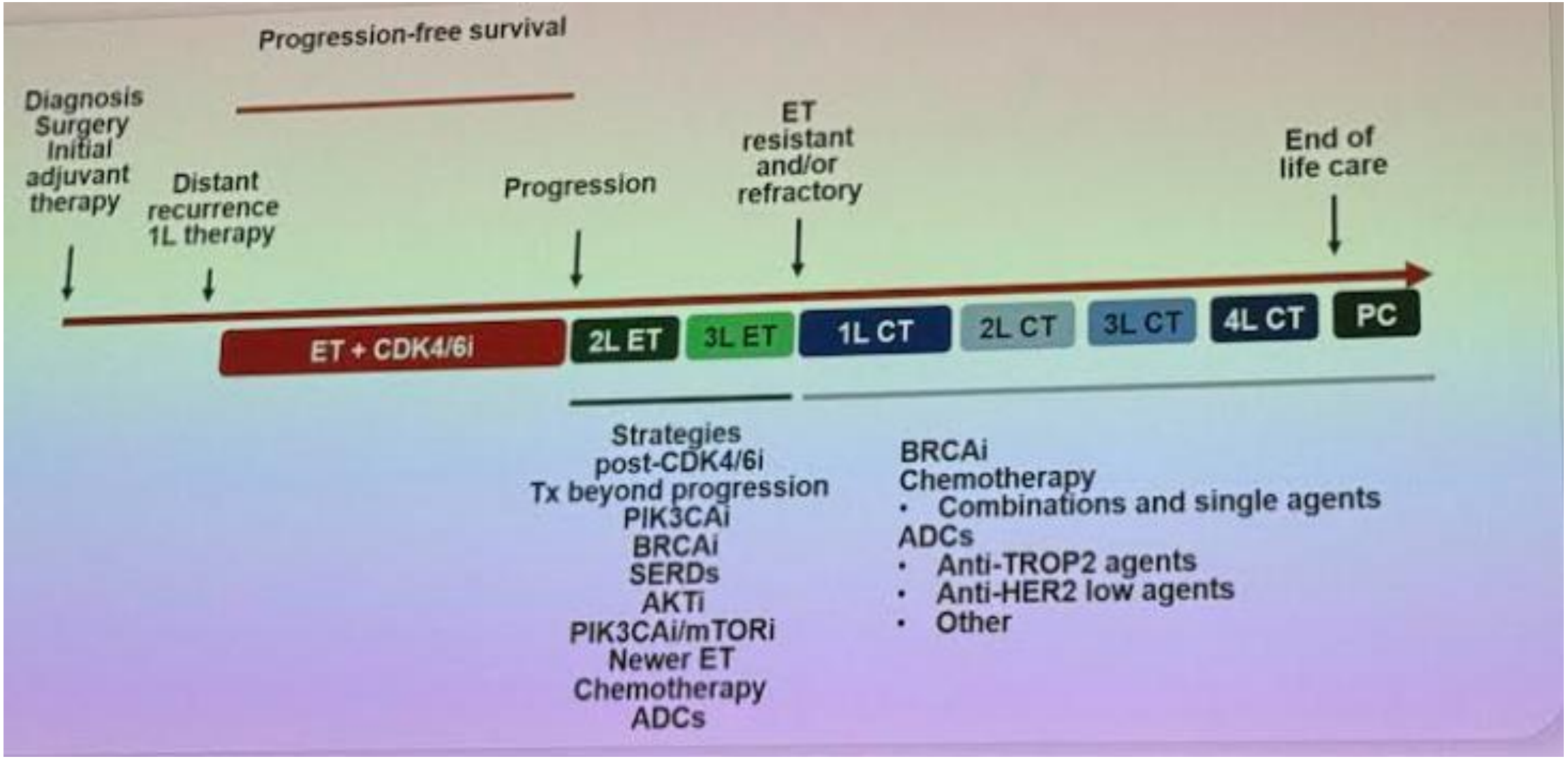
Overall Survival ITT Population

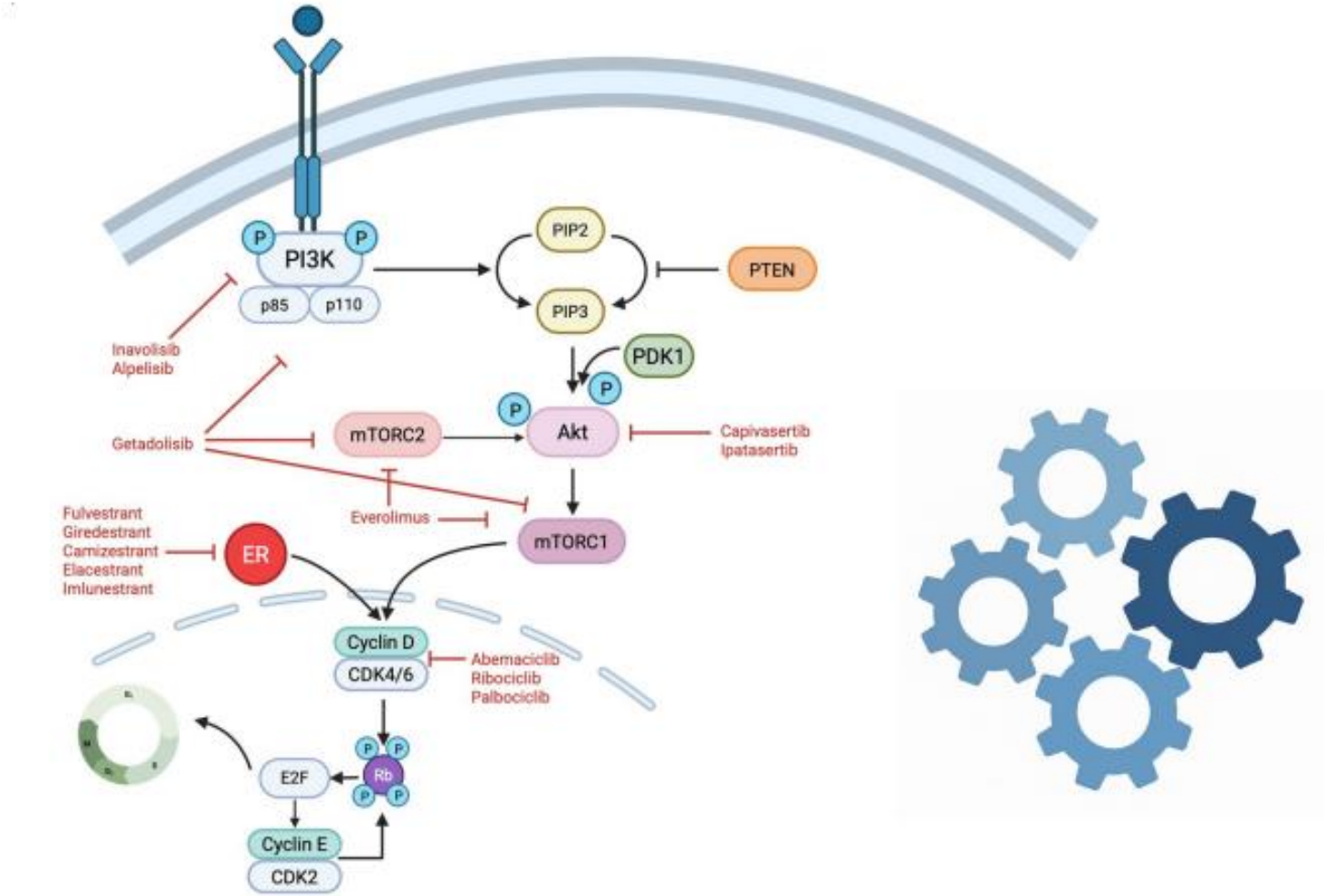
	Abemaciclib + NSAI	Placebo + NSAI
Median, (months)	66.8	53.7
Events	198	116
Patients	328	165
HR (95% CI; *P*value)	0.804 (0.637-1.015; 0.0664)	



Muchas progresaran



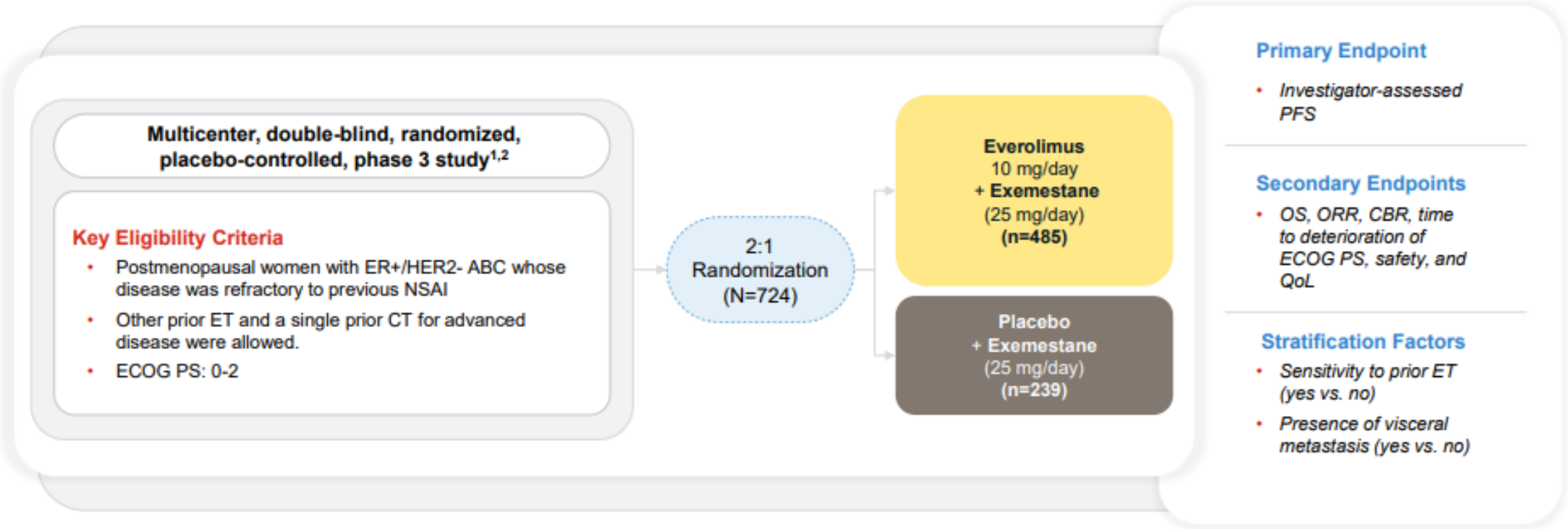

Progression-free survival
Diagnosis
Surgery
Initial
adjuvant
therapy
Distant
recurrence
1L therapy
Progression
ET
resistant
and/or
refractory
End of
life care
ET + CDK4/6i
2L ET
3L ET
1L CT
2L CT
3L CT
4L CT
PC
Strategies
post-CDK4/6i
Tx beyond progression
PIK3CAi
BRCAi
SERDs
AKTi
PIK3CAi/mTORi
Newer ET
Chemotherapy
ADCs
BRCAi
Chemotherapy
• Combinations and single agents
ADCs
• Anti-TROP2 agents
• Anti-HER2 low agents
• Other



A Gennari

No se observaron alteraciones en PIK3CA, AKT1 ni PTEN (vía PI3K)

BOLERO-2
Study Design

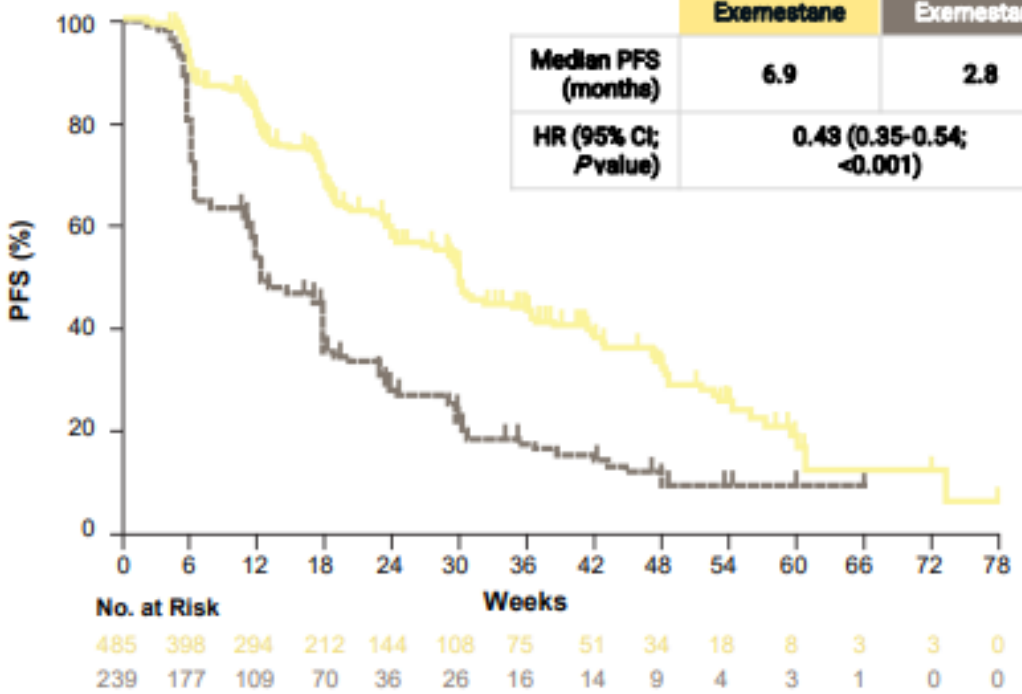


N Engl J Med. 2012;366(6):520. Epub 2011 Dec 7.

BOLERO-2
*Efficacy Results**

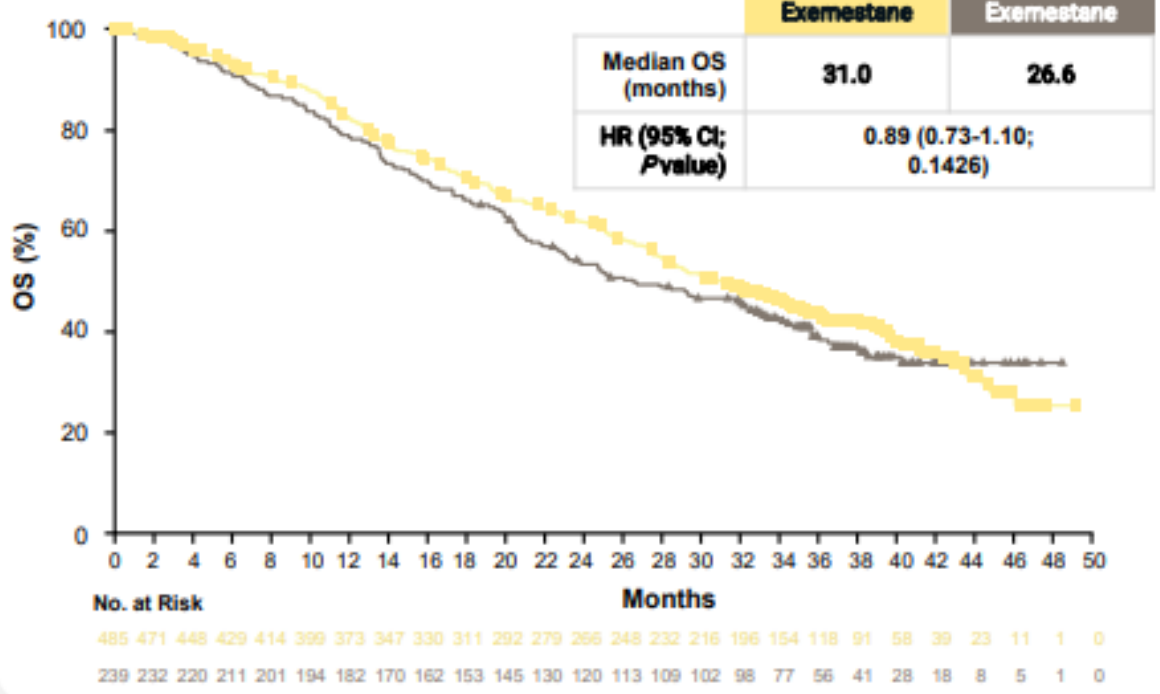
PFS Analysis[1a]

	Everolimus + Exemestane	Placebo + Exemestane
Median PFS (months)	6.9	2.8
HR (95% CI; *P* value)	0.43 (0.35-0.54; <0.001)	



OS Analysis[2]

	Everolimus + Exemestane	Placebo + Exemestane
Median OS (months)	31.0	26.6
HR (95% CI; *P* value)	0.89 (0.73-1.10; 0.1426)	

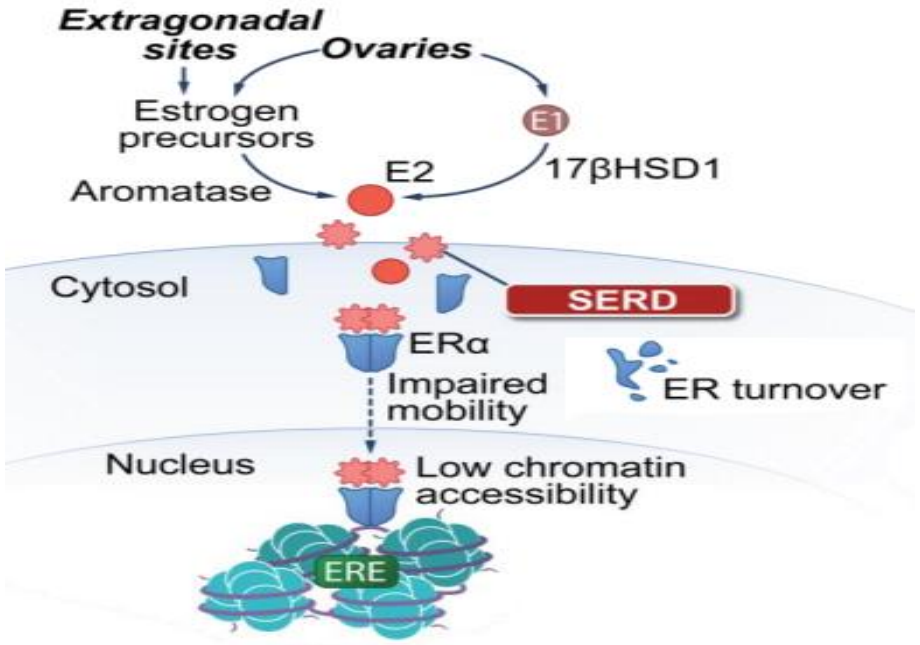


Everolimus + exemestane demonstrated a significantly longer mPFS than exemestane alone in patients with ER+/HER2- ABC. There was no statistically significant improvement in mOS

N Engl J Med. 2012;366(6):520. Epub 2011 Dec 7.

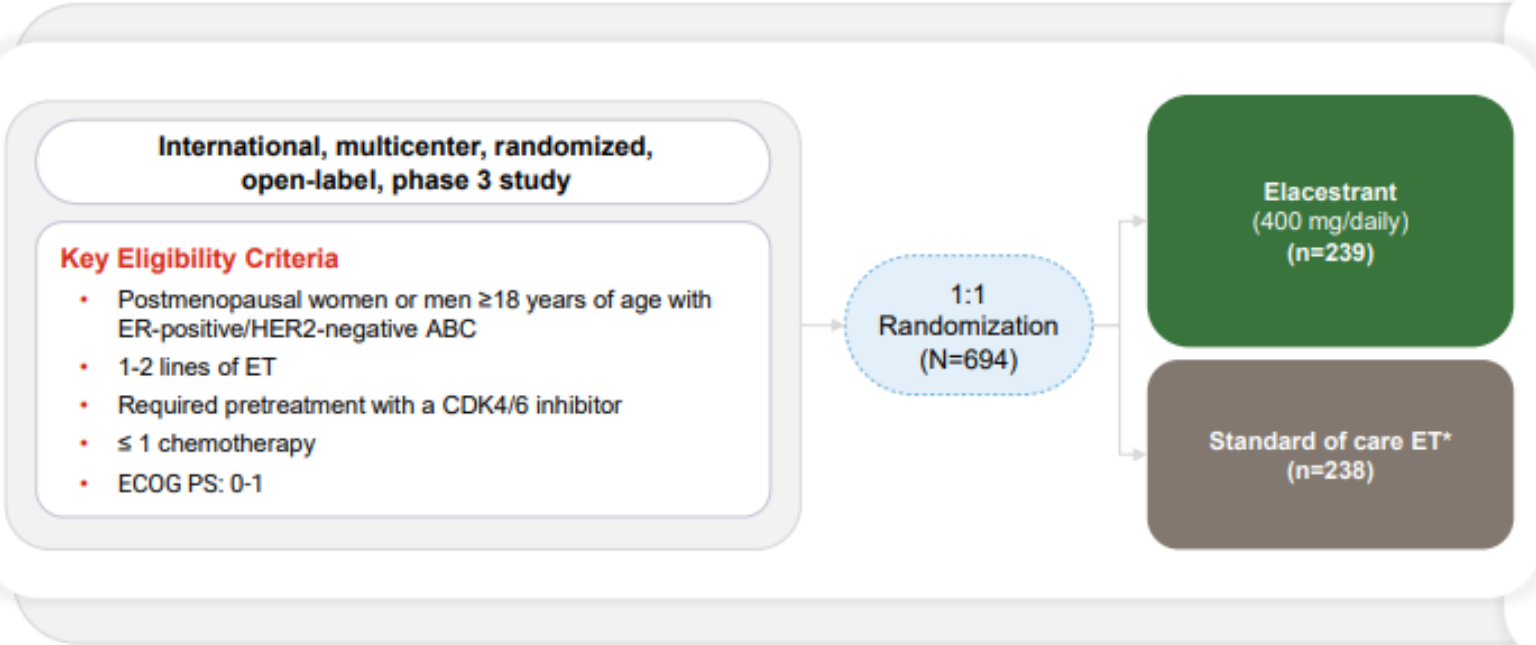
Mutación ESR1

- El 30 % de los cánceres de mama metastásicos con receptores de estrógeno (RE) positivos pueden presentar mutaciones activadoras en el dominio de unión a estrógeno del gen que codifica para RE (*ESR1*)
- *Las opciones aceptables incluyen el SERD* elacestrant o el antagonista de estrógeno imlunestrant , ambos con aprobación regulatoria en los Estados Unidos para esta indicación



JAMA Oncol. 2016;2(10):1310.

EMERALD
Study Design



Primary Endpoint

- *Investigator-assessed PFS (overall population and in patients with detectable ESR1 mutations)*

Secondary Endpoints

- *OS, ORR, duration of response, CBR, safety/tolerability*

Stratification Factors

- *ESR1 mutational status*
- *Presence of visceral metastases*
- *Previous treatment with fulvestrant*

*Per investigator's choice of fulvestrant, anastrozole, letrozole, or exemestane monotherapy dosed according to the labeling.

Clinical Trial Identification: NCT03778931.

Abbreviations: ABC=Advanced Breast Cancer; AI=Aromatase Inhibitor; CDK=Cyclin-dependent Kinase; ET=Endocrine Therapy;HER2=Human Epidermal Growth Factor Receptor 2; HR=hormone receptor; ORR=Objective Response Rate; OS=Overall Survival; PFS=Progression-Free Survival; SOC=Standard of Care.

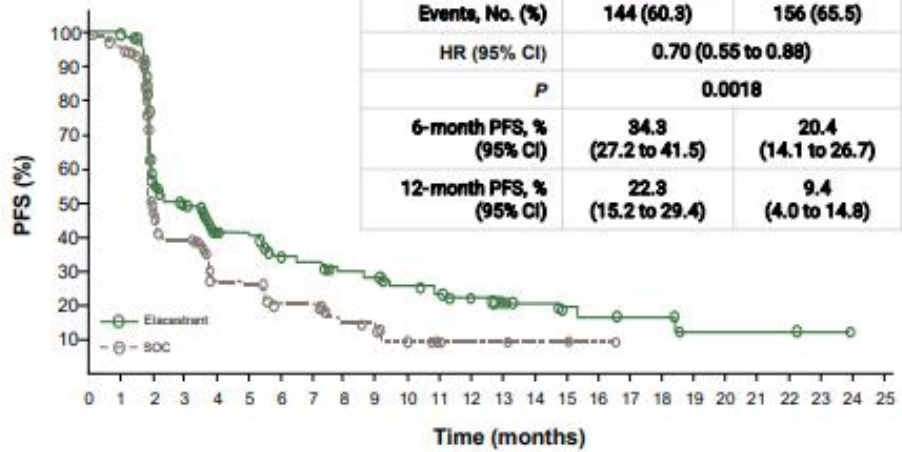
References: Bidard FC, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. *J Clin Oncol.* 2022;40(28):3246-3256.

EMERALD

*Efficacy Results**

PFS (in ALL patients)

	Elacestrant (n = 239)	SOC (n = 238)
Events, No. (%)	144 (60.3)	156 (65.5)
HR (95% CI)	0.70 (0.55 to 0.88)	
P	0.0018	
6-month PFS, % (95% CI)	34.3 (27.2 to 41.5)	20.4 (14.1 to 26.7)
12-month PFS, % (95% CI)	22.3 (15.2 to 29.4)	9.4 (4.0 to 14.8)

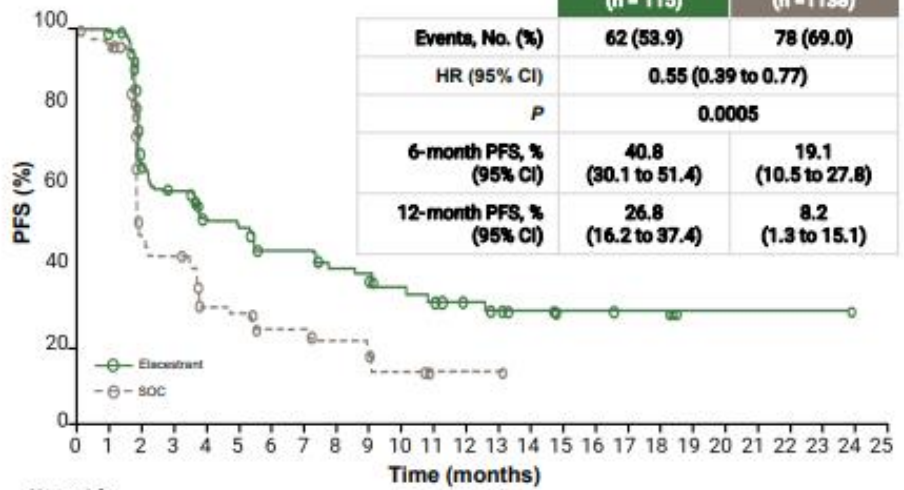


No. at risk

Elacestrant	239	223	106	89	60	57	42	40	34	33	27	24	19	13	11	8	7	6	6	2	2	2	2	1	0
SOC	238	206	84	68	39	38	25	25	16	15	7	4	3	3	2	2	1	0							

PFS (patients with detectable *ESR1* mutation)

	Elacestrant (n = 115)	SOC (n =1138)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	0.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)



No. at risk

Elacestrant	115	105	54	46	35	33	26	26	21	20	16	14	11	9	7	5	5	4	4	1	1	1	1	1	0
SOC	113	99	39	34	19	18	12	12	9	9	4	1	1	1	0										

Elacestrant demonstrated a significant improvement in PFS versus SOC therapy in ER-positive, HER2-negative, advanced or metastatic breast cancer in the second- or third-line setting

*Data cut-off: September 6, 2021.

Clinical Trial Identification: NCT03778931.

Abbreviations: CI=Confidence Interval; HR=Hazard Ratio; PFS=Progression-Free Survival; SOC=standard of care.

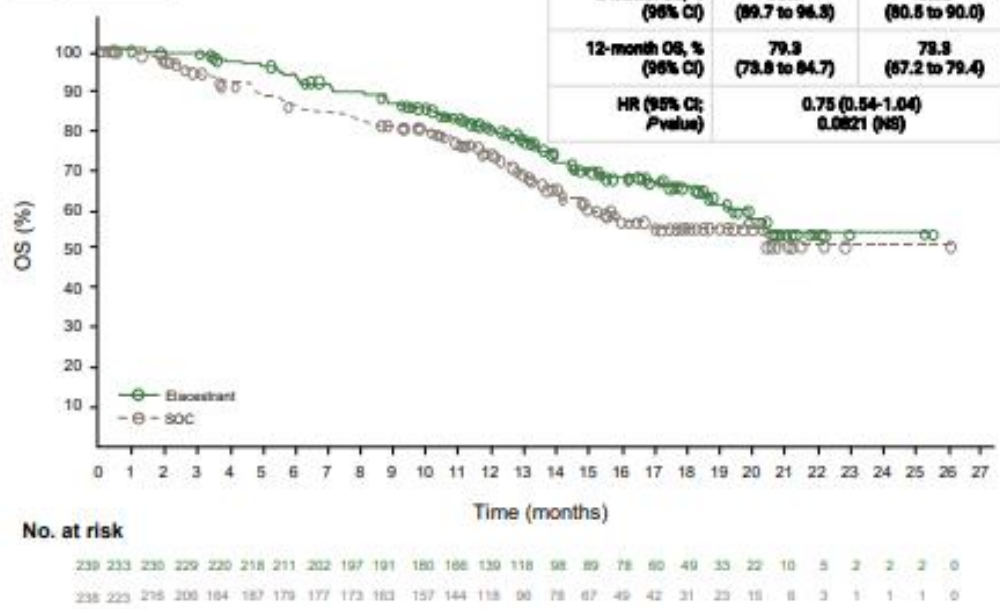
Reference: Ridard FC, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. *J Clin Oncol* 2022;40(28):3246-3256.

EMERALD

*Efficacy Results**

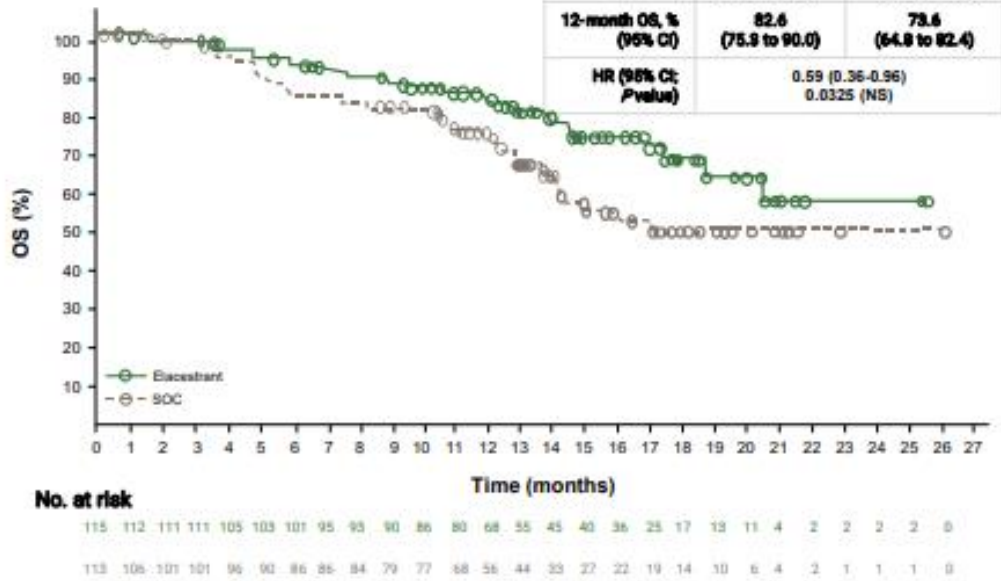
Interim analysis overall survival (All patients)

	Elacestrant (n = 239)	SOC (n = 238)
6-month OS, % (95% CI)	93.0 (89.7 to 96.3)	85.2 (80.5 to 90.0)
12-month OS, % (95% CI)	79.3 (75.8 to 84.7)	75.8 (67.2 to 79.4)
HR (95% CI; *P* value)	0.75 (0.54-1.04) 0.0821 (NS)	



Interim analysis of overall survival (Patients with detectable *ESR1* mutation)

	Elacestrant (n = 115)	SOC (n = 113)
6-month OS, % (95% CI)	92.8 (88.0 to 97.6)	84.4 (77.3 to 91.4)
12-month OS, % (95% CI)	82.6 (75.9 to 90.0)	73.6 (64.8 to 82.4)
HR (95% CI; *P* value)	0.59 (0.36-0.96) 0.0325 (NS)	



The differences in overall survival in this interim analysis were not statistically significant on the basis of the allocated two-sided alpha level of 0.0001. The final OS results will be provided in the future when data are mature.

*Data cut-off: September 6, 2021.

Clinical Trial Identification: NCT03778931

Abbreviations: CI=Confidence Interval; HR=Hazard Ratio; NS=nonsignificant; OS=Overall Survival; SOC=standard of care.

Reference: Bidard FC, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. *J Clin Oncol* 2022;40(28):3246-3256.

EMERALD

*Safety Results (Overall Population)**

AEs[a] ≥10% in either arm, n (%)	Elacestrant (n=237)		SOC (n=229)	
	Any Grade	Grade 3+4[b]	Any Grade	Grade 3+4
Any AEs	218 (92.0)	64 (27.0)	197 (86.0)	47 (20.5)
Nausea	83 (35.0)[c]	6 (2.5)	43 (18.8)	2 (0.9)
Fatigue	45 (19.0)	2 (0.8)	43 (18.8)	2 (0.9)
Vomiting	45 (19.0)[d]	2 (0.8)	19 (8.3)	0 (0.0)
Decreased appetite	35 (14.8)	2 (0.8)	21 (9.2)	1 (0.4)
Arthralgia	34 (14.3)	2 (0.8)	37 (16.2)	0 (0.0)
Diarrhea	33 (13.9)	0 (0.0)	23 (10.0)	2 (0.9)
Back pain	33 (13.9)	6 (2.5)	22 (9.6)	1 (0.4)
AST increased	31 (13.1)	4 (1.7)	28 (12.2)	2 (0.9)
Headache	29 (12.2)	4 (1.7)	26 (11.4)	0 (0.0)
Constipation	29 (12.2)	0 (0.0)	15 (6.6)	0 (0.0)
Hot flush	27 (11.4)	0 (0.0)	19 (8.3)	0 (0.0)
Dyspepsia	24 (10.1)	0 (0.0)	6 (2.6)	0 (0.0)
ALT increased	22 (9.3)	5 (2.1)	23 (10.0)	1 (0.4)

Warnings & Precautions

Elacestrant can cause dyslipidemia and embryo-fetal toxicity. For more information, please refer to the full US prescribing information at https://rxmenarinistemline.com/ORSERDU_elacestrant_Full_Prescribing_Information.pdf

Elacestrant exhibited manageable toxicity with most AEs of grade 1 or 2 severity. The most frequent AE was nausea and was of grade 3 severity in 2.5% of patients.

*Data cut-off: September 6, 2021.

Clinical Trial Identification: NCT03778931.

Abbreviations: AE=Adverse Event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; SOC=Standard of Care.

[a]Preferred terms were coded using the Medical Dictionary for Regulatory Activities version 23.0

[b]AE severity was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0.

[c]Grade 1 nausea, n=59 (24.9%); grade 2 nausea, n=18 (7.6%); grade 3 nausea, n=6 (2.5%); and no patients experienced grade 4 nausea. Percentages reflect maximum grade experienced.

[d]Grade 1 vomiting, n=36 (15.2%); grade 2 vomiting, n=7 (3.0%); grade 3 vomiting, n=2 (0.8%); and no patients experienced grade 4 vomiting. Percentages reflect maximum grade experienced.

Reference: Bidard FC, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. *J Clin Oncol.* 2022;40(28):3246-3256.

The NEW ENGLAND JOURNAL of MEDICINE

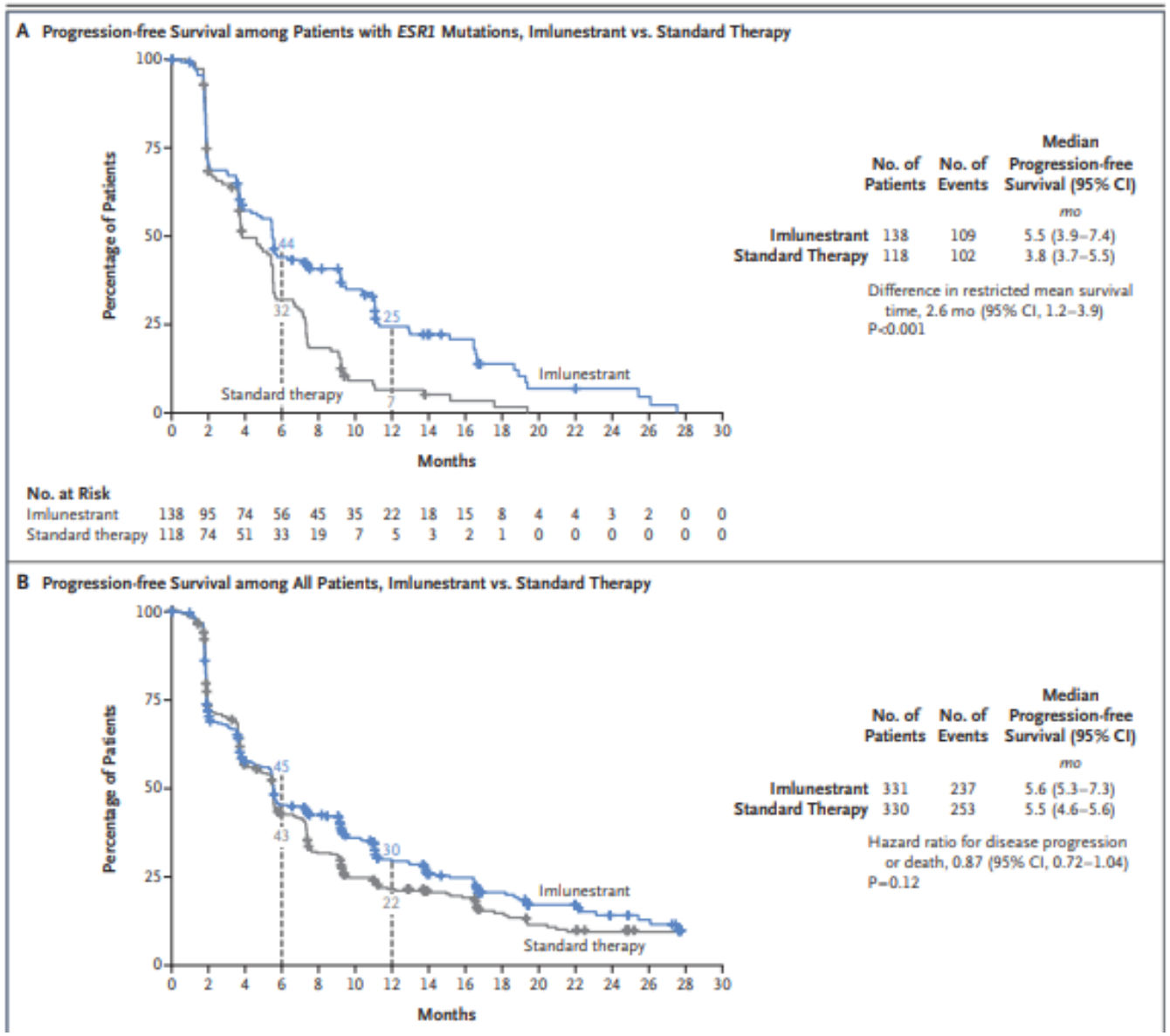
ORIGINAL ARTICLE

Imlunestrant with or without Abemaciclib in Advanced Breast Cancer

En un ensayo aleatorizado (EMBER-3), 874 pacientes con cáncer de mama avanzado

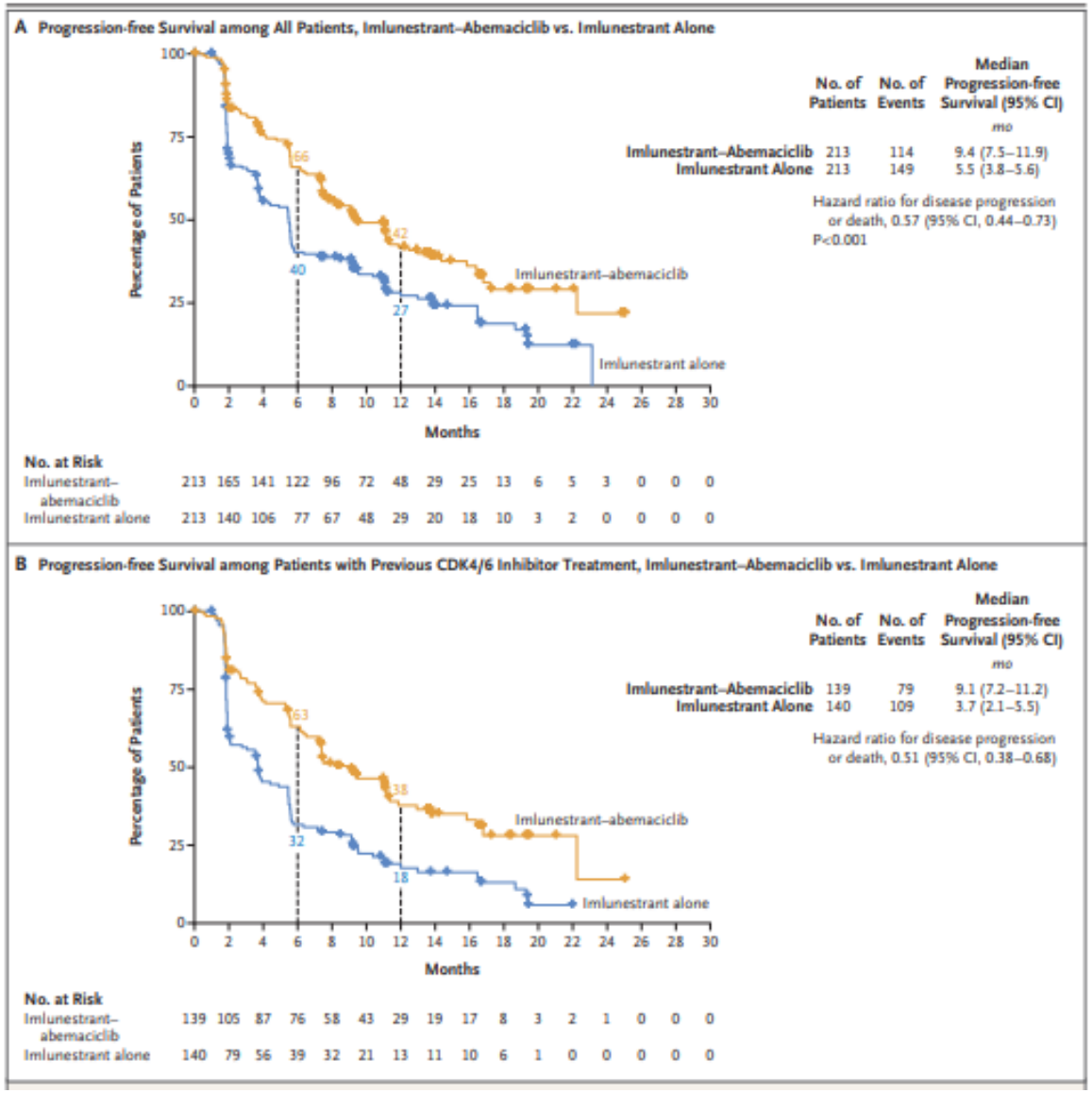
Fueron asignadas aleatoriamente a imlunestrant , tratamiento estándar (exemestano o fulvestrant) o imlunestrant-abemaciclib.

n engl j med 392;12 nejm.org March 27, 2025



Entre las pacientes con mutaciones *ESR1* , imlunestrant mejoró la mediana de la supervivencia libre de progresión (SLP) en comparación con el tratamiento estándar (5,5 frente a 3,8 meses)

n engl j med 392;12 nejm.org March 27, 2025

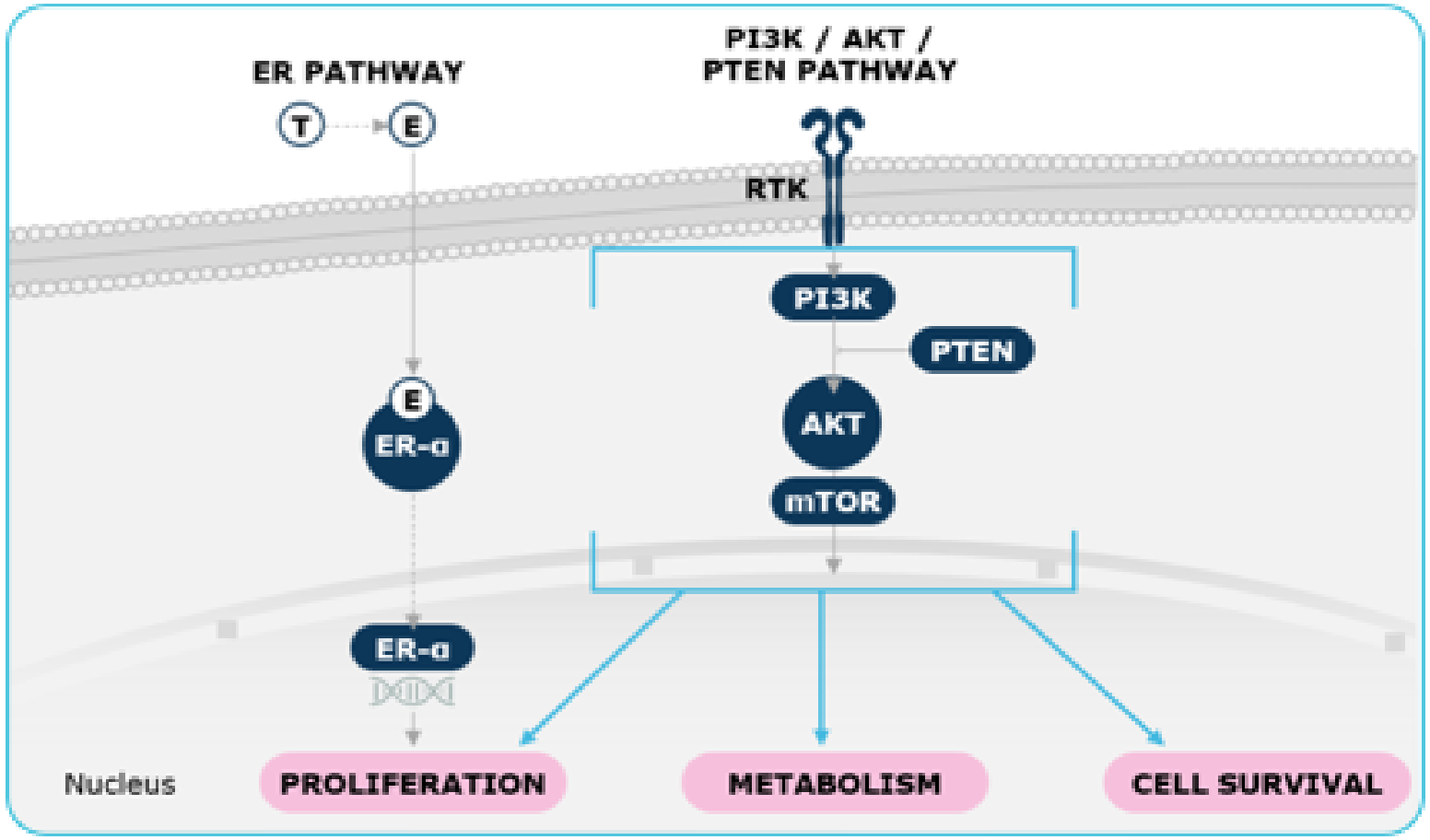


SLP en una población que incluía cánceres con mutación *ESR1* y cánceres de tipo salvaje (9,4 frente a 5,5 meses; HR 0,57, IC del 95 % 0,44-0,73)

n engl j med 392;12 nejm.org March 27, 2025

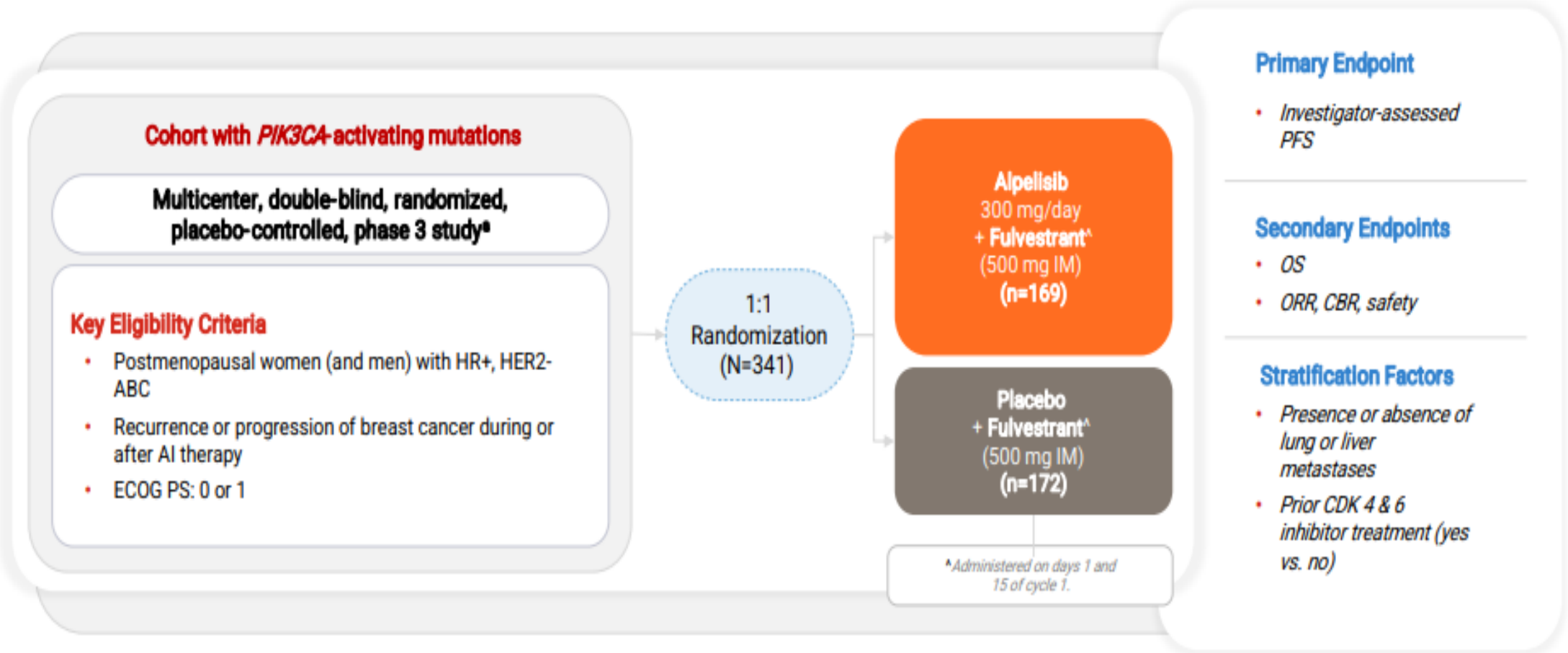
Los caminos de señal de PI3K/AKT/PTEN, juegan un rol importante en la proliferación, sobrevida y metabolismo celular

PI3K/AKT/PTEN signalling pathway in BC[4]



Adapted from: Alves CL, and Ditzel HJ. *Int J Mol Sci.* 2023;24:4522.

SOLAR-1
Study Design

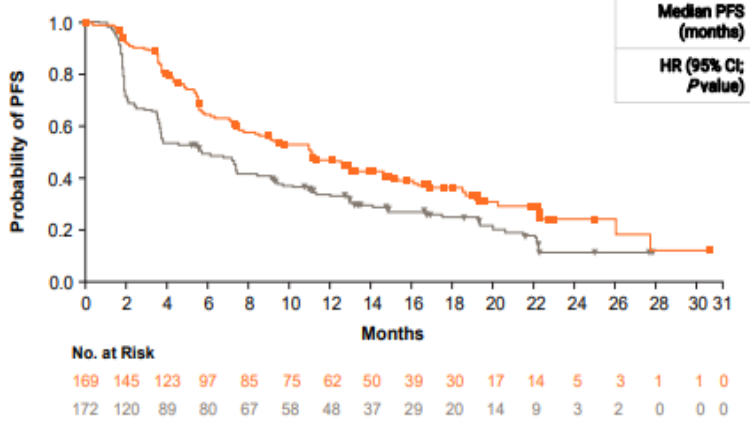


N Inglés J Med. 2019;380(20):1929.

SOLAR-1
*Efficacy Results**

Investigator-Assessed PFS (Cohort With *PIK3CA*-Mutated Cancer)

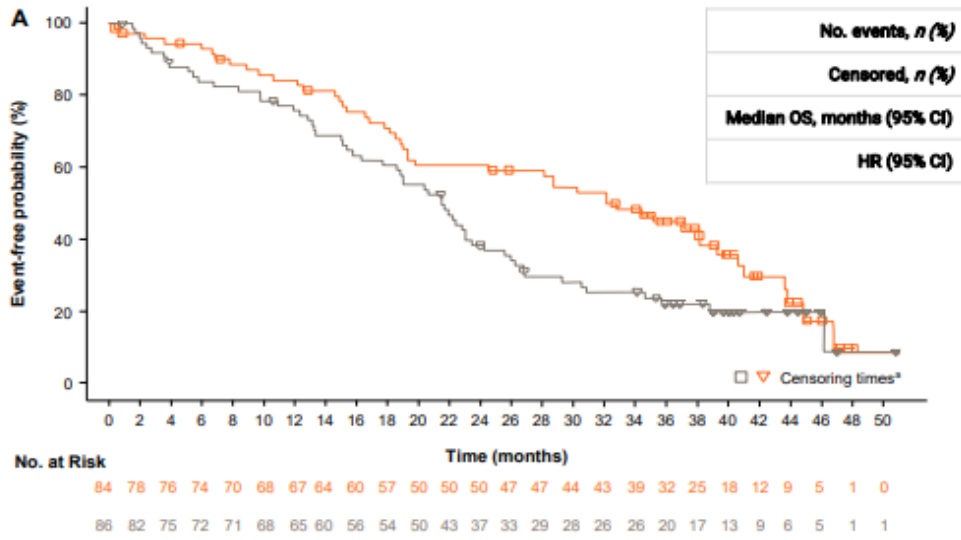
	Alpelisib + Fulvestrant	Placebo + Fulvestrant
Median PFS (months)	11.0	5.7
HR (95% CI; *P* value)	0.65 (0.50-0.85; <0.001)	



Alpelisib + fulvestrant demonstrated a significantly longer mPFS than fulvestrant alone in patient ABC with a PIK3CA mutation

Overall Survival (Cohort With PIK3CA-Mutated Cancer)

	Alpelisib + FUL (*n* = 84)	Placebo + FUL (*n* = 86)
No. events, *n* (%)	47 (56.0)	58 (67.4)
Censored, *n* (%)	37 (44.0)	28 (32.6)
Median OS, months (95% CI)	37.2 (28.7-43.6)	22.8 (19.0-26.8)
HR (95% CI)	0.68 (0.46-1.00)	



Although the analysis did not cross the prespecified boundary for statistical significance, there was a 7.9-month numeric improvement in median OS when alpelisib was added to fulvestrant treatment of patients with PIK3CA mutated, HR+, HER2- ABC

N Inglés J Med. 2019;380(20):1929.

SOLAR-1
*Safety Results**

25% de interrupción del tratamiento

AEs ≥20% in either arm, n (%)	Alpelisib + Fulvestrant (n=284)		Placebo + Fulvestrant (n=287)	
	Any Grade	Grade 3+4	Any Grade	Grade 3+4
Any AEs	282 (99.3)	216 (76)	264 (92.0)	102 (35.5)
Hyperglycemia[a]	181 (63.7)	104 (36.6)	28 (9.8)	2 (0.7)
Diarrhea[b]	164 (57.7)	19 (6.7)	45 (15.7)	1 (0.3)
Nausea[b]	127 (44.7)	7 (2.5)	64 (22.3)	1 (0.3)
Decreased appetite	101 (35.6)	2 (0.7)	30 (10.5)	1 (0.3)
Rash[c]	101 (35.6)	28 (9.9)	17 (5.9)	1 (0.3)
Vomiting[b]	77 (27.1)	2 (0.7)	28 (9.8)	1 (0.3)
Weight loss	76 (26.8)	11 (3.9)	6 (2.1)	0
Stomatitis	70 (24.6)	7 (2.5)	18 (6.3)	0
Fatigue	69 (24.3)	10 (3.5)	49 (17.1)	3 (1.0)
Asthenia	58 (20.4)	5 (1.8)	37 (12.9)	0

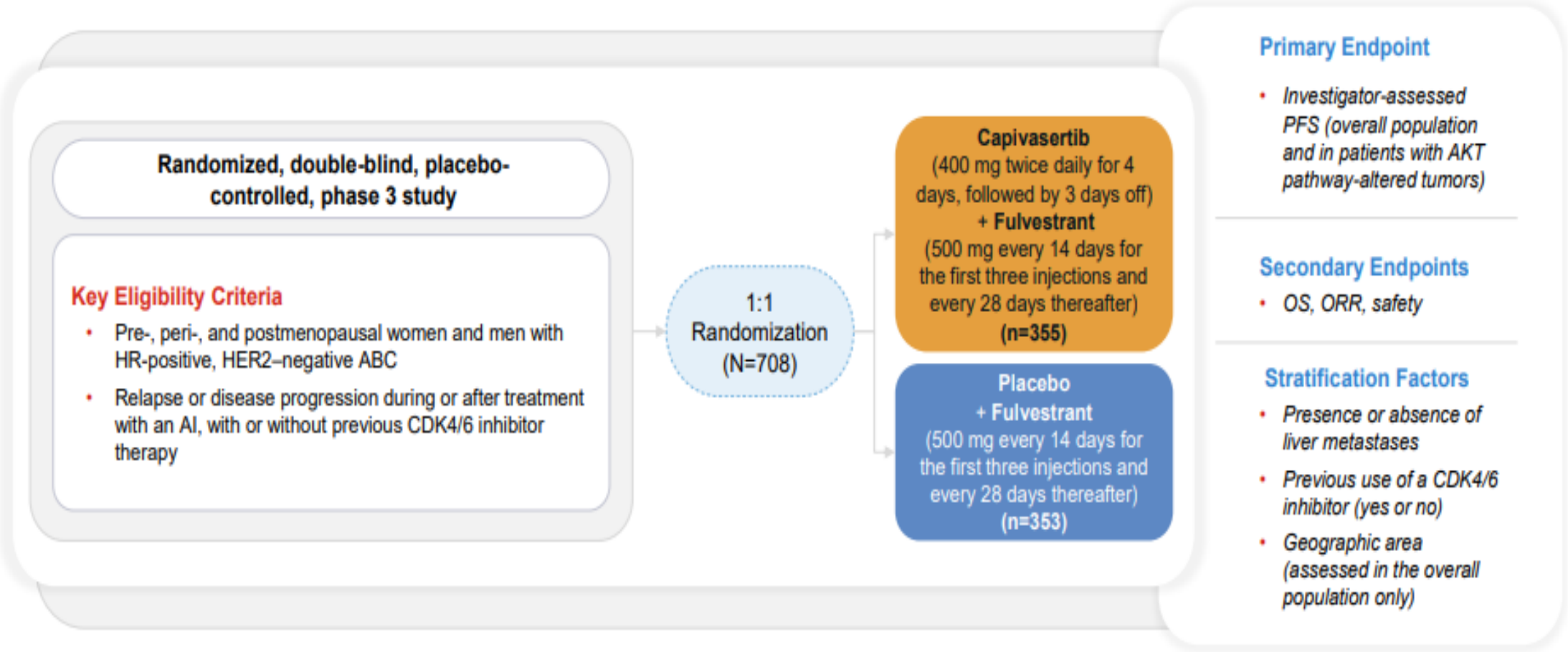
Warnings & Precautions

Alpelisib can cause severe hypersensitivity, severe cutaneous adverse reactions, hyperglycemia, pneumonitis, diarrhea, and embryo-fetal toxicity. For more information, please refer to the full US prescribing information at https://www.novartis.us/sites/www.novartis.us/files/piqray.pdf.

In the alpelisib + fulvestrant arm, the most common Any Grade AEs were hyperglycemia, diarrhea, nausea, decreased appetite and rash

N Inglés J Med. 2019;380(20):1929.

CAPItello-291
Study Design

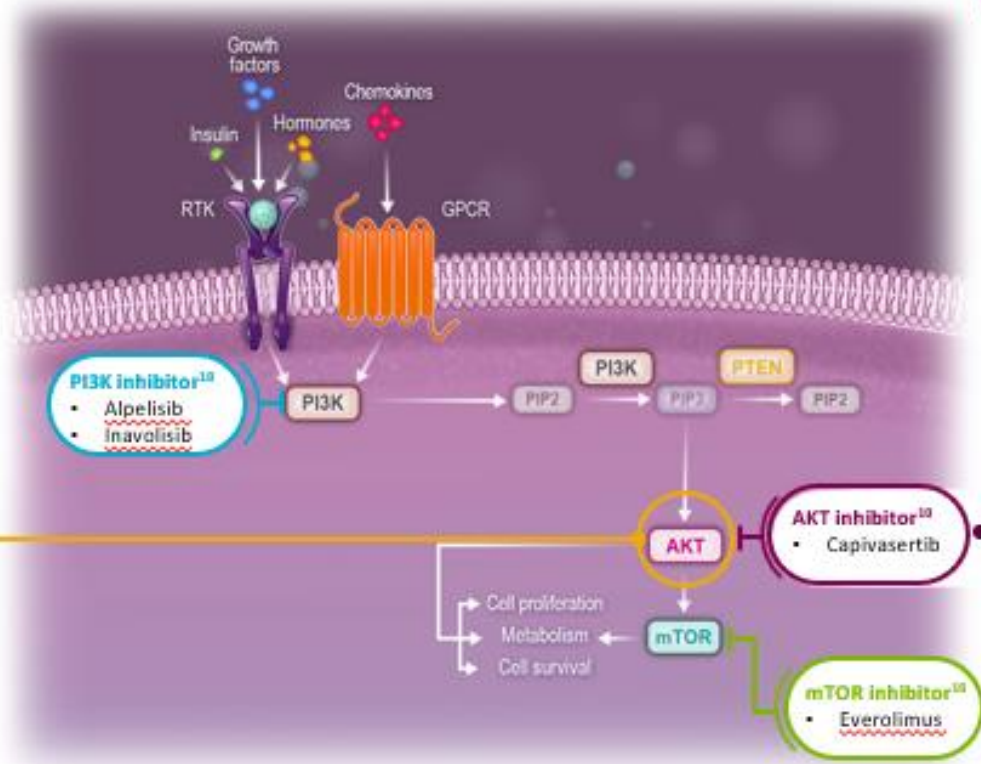


Lancet Oncol. 2024;25(9):1231

Capivasertib is a potent, selective inhibitor of all three AKT isoforms

1 AKT is a key node within the PI3K/AKT/PTEN pathway

Inhibition of the AKT node can disrupt aberrant signalling within, and downstream of, the PI3K/AKT/PTEN pathway[1,2]



Adapted from: Miricescu D, et al. *Int J Mol Sci*. 2021;22:170.[11]

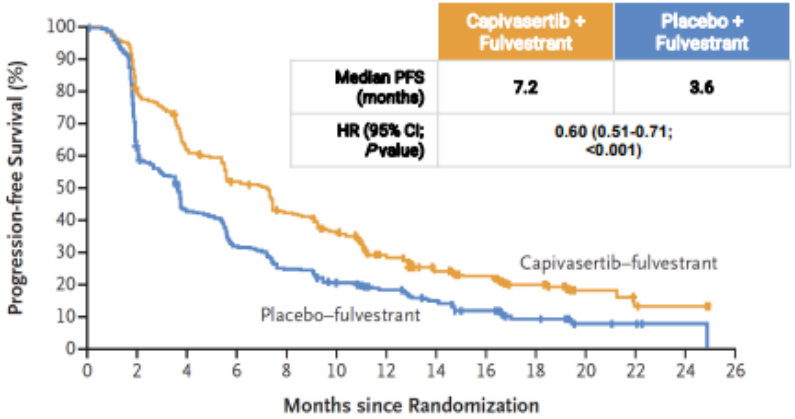
2 Capivasertib is an ATP-competitive inhibitor of all three AKT isoforms (*AKT1/AKT2/AKT3*)[3,4]

Co-targeting the ER and PI3K/AKT/PTEN pathways through the combination of capivasertib + ET (fulvestrant) is a viable strategy to optimise ET benefit and signalling in patients with pathway-altered HR-positive aBC[5–9]

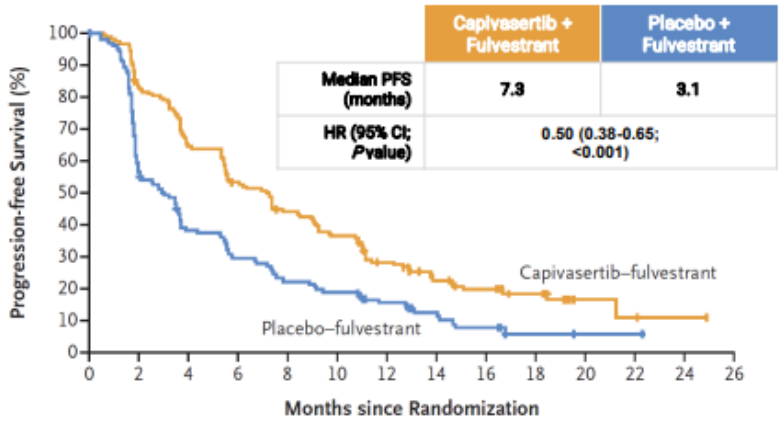
CAPItello-291

*Efficacy Results**

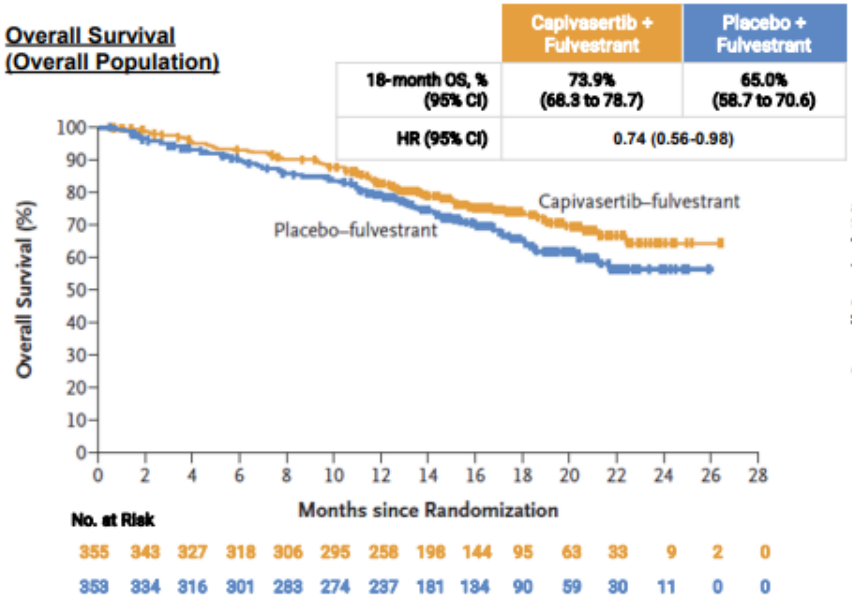
Investigator-Assessed PFS (Overall Population)



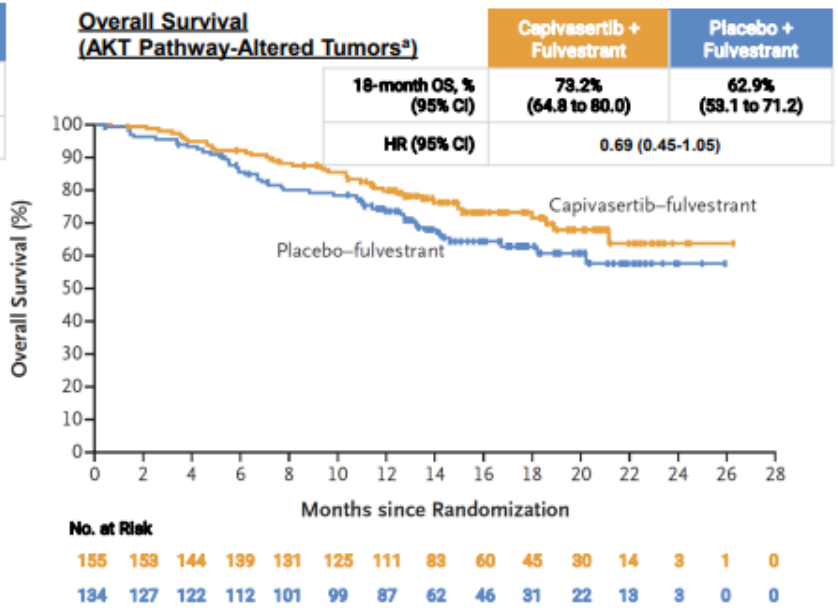
Investigator-Assessed PFS (AKT Pathway-Altered Tumors[a])



Overall Survival (Overall Population)



Overall Survival (AKT Pathway-Altered Tumors[a])



Lancet Oncol. 2024;25(9):1231

CAPItello-291

Safety Results (Overall Population),a*

AEs ≥10% in either arm, n (%)	Capivasertib + Fulvestrant (n=355)		Placebo + Fulvestrant (n=350)	
	Any Grade	Grade 3+4	Any Grade	Grade 3+4
Any AEs	343 (96.6)	148 (41.7)	288 (82.3)	54 (15.4)
Diarrhea	257 (72.4)	33 (9.3)	70 (20.0)	1 (0.3)
Rash[b]	135 (38.0)	43 (12.1)	25 (7.1)	1 (0.3)
Nausea	123 (34.6)	3 (0.8)	54 (15.4)	2 (0.6)
Fatigue	74 (20.8)	2 (0.6)	45 (12.9)	2 (0.6)
Vomiting	73 (20.6)	6 (1.7)	17 (4.9)	2 (0.6)
Headache	60 (16.9)	1 (0.3)	43 (12.3)	2 (0.6)
Decreased appetite	59 (16.6)	1 (0.3)	22 (6.3)	2 (0.6)
Hyperglycemia	58 (16.3)	8 (2.3)	13 (3.7)	1 (0.3)
Stomatitis	52 (14.6)	7 (2.0)	17 (4.9)	0 (0.0)
Asthenia	47 (13.2)	4 (1.1)	36 (10.3)	2 (0.6)
Pruritis	44 (12.4)	2 (0.6)	23 (6.6)	0 (0.0)
Anemia	37 (10.4)	7 (2.0)	17 (4.9)	4 (1.1)
Urinary tract infection	36 (10.1)	5 (1.4)	23 (6.6)	0 (0.0)

Warnings & Precautions

Capivasertib can cause hyperglycemia, diarrhea, cutaneous adverse reactions, and embryo-fetal toxicity. For more information, please refer to the full US prescribing information at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/218197s000lbl.pdf

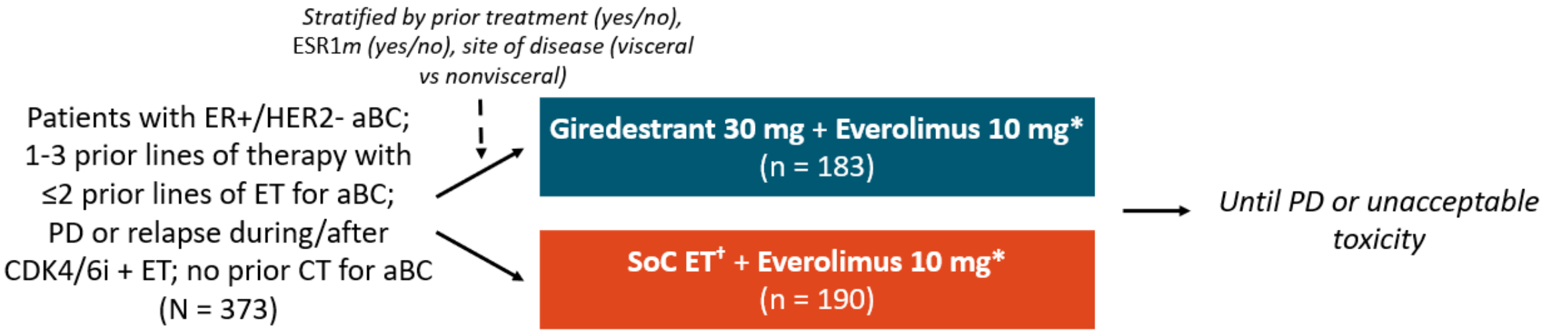
Among patients receiving capivasertib, diarrhea, rash and nausea were the most common adverse events of any grade, occurring in 72.4%, 38.0%, and 34.6% of patients, respectively

*Data cut-off: August 15, 2022.

Lancet Oncol. 2024;25(9):1231

evERA BC: Study Design

- Global, open-label, randomized phase III trial

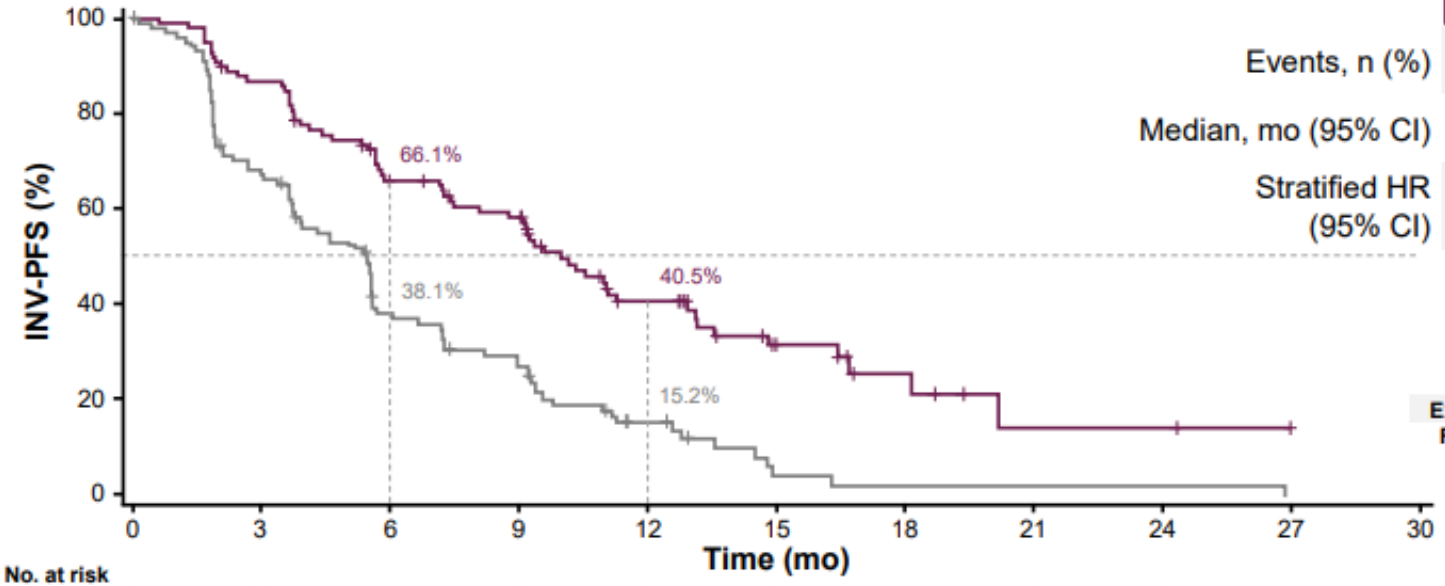


*Dexamethasone mouthwash prophylaxis and treatment strongly recommended per SWISH protocol.
†Exemestane/fulvestrant/tamoxifen.

- **Primary endpoints:** INV-PFS in patients whose tumors had *ESR1*m and in ITT population
- **Secondary endpoints:** OS, INV-assessed ORR, DoR

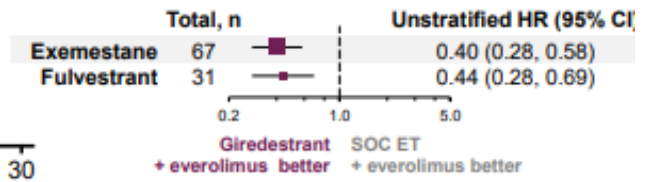
Mayer. ESMO 2025. Abstr LBA16.

Co-primary endpoint – INV-PFS in the *ESR1*m population



	Giredestrant + everolimus n = 102	SOC ET + everolimus n = 105
Events, n (%)	63 (61.8)	89 (84.8)
Median, mo (95% CI)	**9.99** (8.08, 12.94)	**5.45** (3.75, 5.62)
Stratified HR (95% CI)	**0.38** (0.27, 0.54); p < 0.0001	

Exploratory analysis: INV-PFS by SOC ET

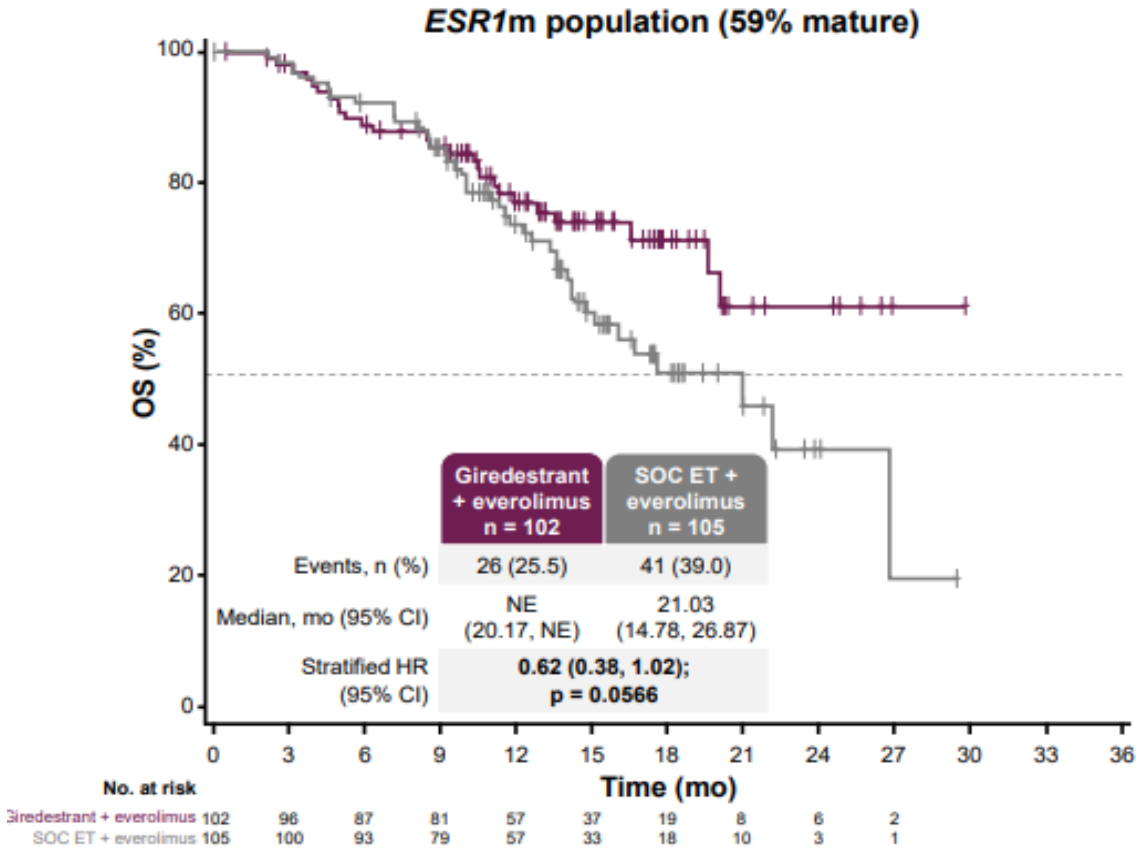


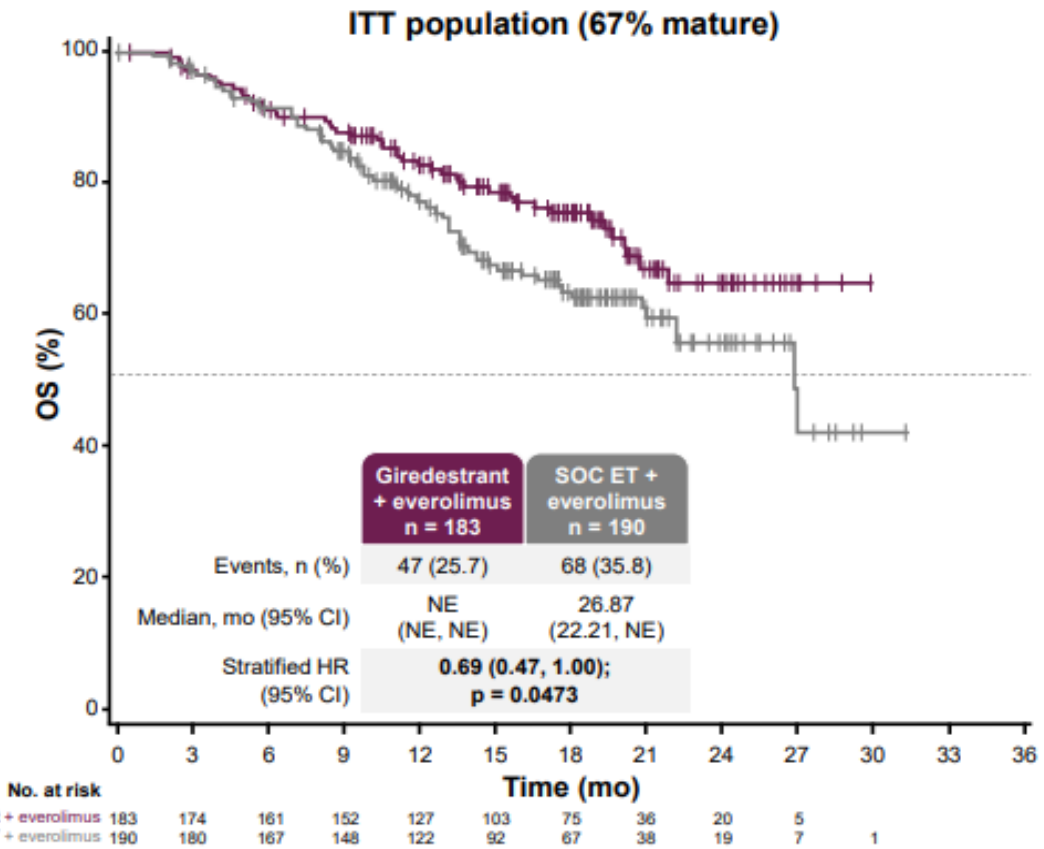
Combination therapy with giredestrant + everolimus led to a clinically meaningful 62% reduction in the risk of progression or death in patients with *ESR1*m

Data cutoff: 16 July 2025. PFS by blinded independent radiologist was similar to INV-PFS: Median PFS was 11.14 mo (giredestrant + everolimus) and 5.68 mo (SOC ET + everolimus); stratified HR, 0.49; 95% CI: 0.34, 0.71.
CI, confidence interval; *ESR1*m, *ESR1* mutation; HR, hazard ratio; INV, investigator-assessed; mo, months; PFS, progression-free survival; SOC ET, standard of care endocrine therapy.

Presented by: Erica L. Mayer, MD, MPH.

Interim OS in the *ESR1*m and ITT populations





Data cutoff: 16 July 2025. CI, confidence interval; *ESR1*m, *ESR1* mutation; HR, hazard ratio; ITT, intention to treat; mo, months; NE, not evaluable; OS, overall survival; SOC ET, standard of care endocrine therapy.

Presented by: Erica L. Mayer, MD, MPH.

evERA BC: Safety

- Most common TEAEs in both treatment arms were stomatitis, diarrhea, and anemia

TEAE, %	Giredestrant + Everolimus (n = 182)		SoC ET + Everolimus (n = 186)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Stomatitis	44.5	2.7	45.7	3.2
Diarrhea	26.9	0	21.5	1.1
Anemia	17.6	6.0	12.4	8.6

- n = 7 (3.8%) and n = 1 (0.5%) of patients receiving giredestrant + everolimus and SoC ET + everolimus, respectively, experienced bradycardia (all grade 1/2)

Mayer. ESMO 2025. Abstr LBA16.

Conclusions

- The next-generation oral SERD giredestrant, in combination with everolimus, showed **statistically significant and clinically meaningful improvements in INV-PFS** vs SOC ET + everolimus in ER+, HER2– aBC post-CDK4/6i
  - ***ESR1*m:** 62% reduction in the risk of progression or death (HR **0.38**; median INV-PFS **9.99** vs 5.45 mo)
  - **ITT:** 44% reduction in the risk of progression or death (HR **0.56**; median INV-PFS, **8.77** vs 5.49 mo)
- Consistent benefit with giredestrant + everolimus was seen across key subgroups; ORR and DoR benefits were observed irrespective of *ESR1*m status; OS analyses were immature and favourable
- The safety profile of giredestrant + everolimus was manageable and consistent with the known safety profiles of the individual drugs; there were no unexpected safety findings

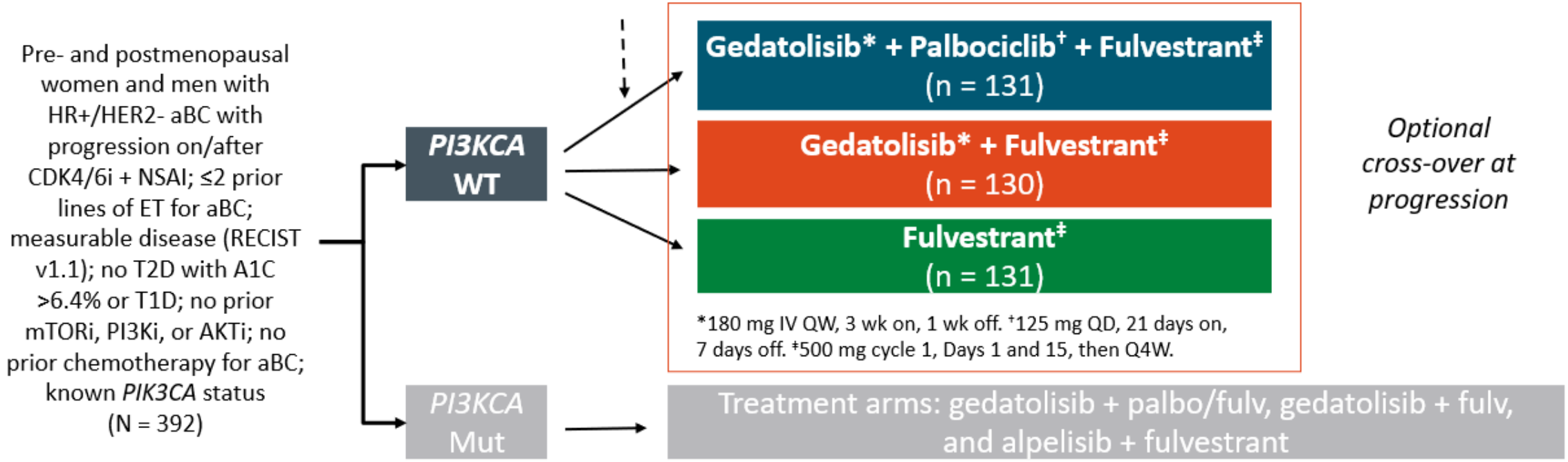
Giredestrant + everolimus may represent a new effective all-oral treatment option in the post-CDK4/6i setting for patients with ER+, HER2– aBC

aBC, advanced breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DoR, duration of response; ER+, oestrogen receptor-positive; *ESR1*m, *ESR1* mutation; HER2–, HER2-negative; HR, hazard ratio; INV-PFS, investigator-assessed progression-free survival; ITT, intention to treat; mo, months; ORR, objective response rate; OS, overall survival; SERD, selective oestrogen receptor antagonist and degrader; SOC ET, standard of care endocrine therapy.

VIKTORIA-1: Study Design

- International, open-label, randomized phase III trial

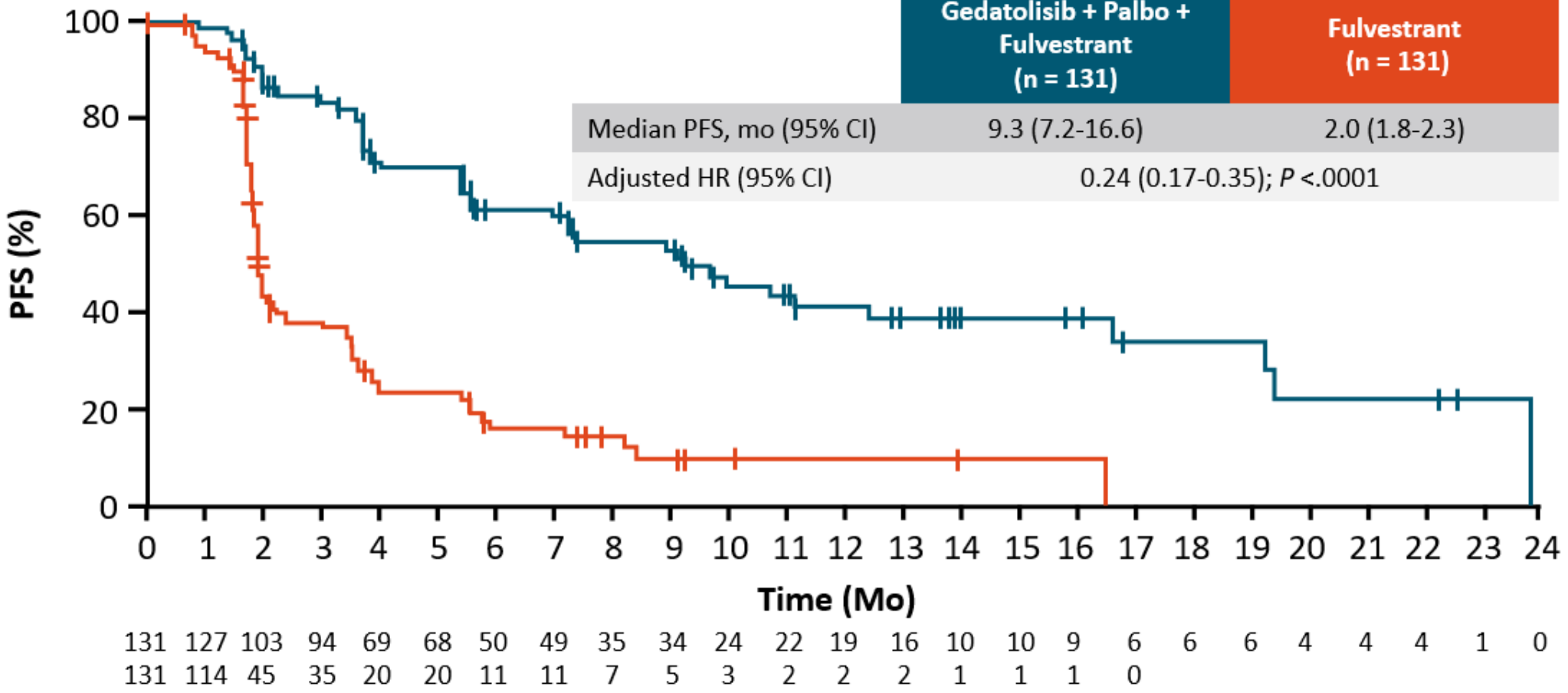
Stratified by lung/liver metastases (yes vs no), TTP on last prior therapy (≤ vs >6 months), and region (US/Canada vs ROW)



- **Co-primary endpoints:** PFS (by BICR) of triplet regimen vs fulvestrant and PFS (by BICR) of doublet regimen vs fulvestrant
- **Key secondary endpoints:** OS, response, safety, QoL

Hurvitz. ESMO 2025. Abstr LBA17. NCT05501886.

VIKTORIA-1: PFS With Gedatolisib + Palbo + Fulvestrant vs Fulvestrant (Coprimary Endpoint)



	Gedatolisib + Palbo + Fulvestrant (n = 131)	Fulvestrant (n = 131)
Median PFS, mo (95% CI)	9.3 (7.2-16.6)	2.0 (1.8-2.3)
Adjusted HR (95% CI)	0.24 (0.17-0.35); *P* <.0001	

Hurvitz. ESMO 2025. Abstr LBA17. Reproduced with permission.

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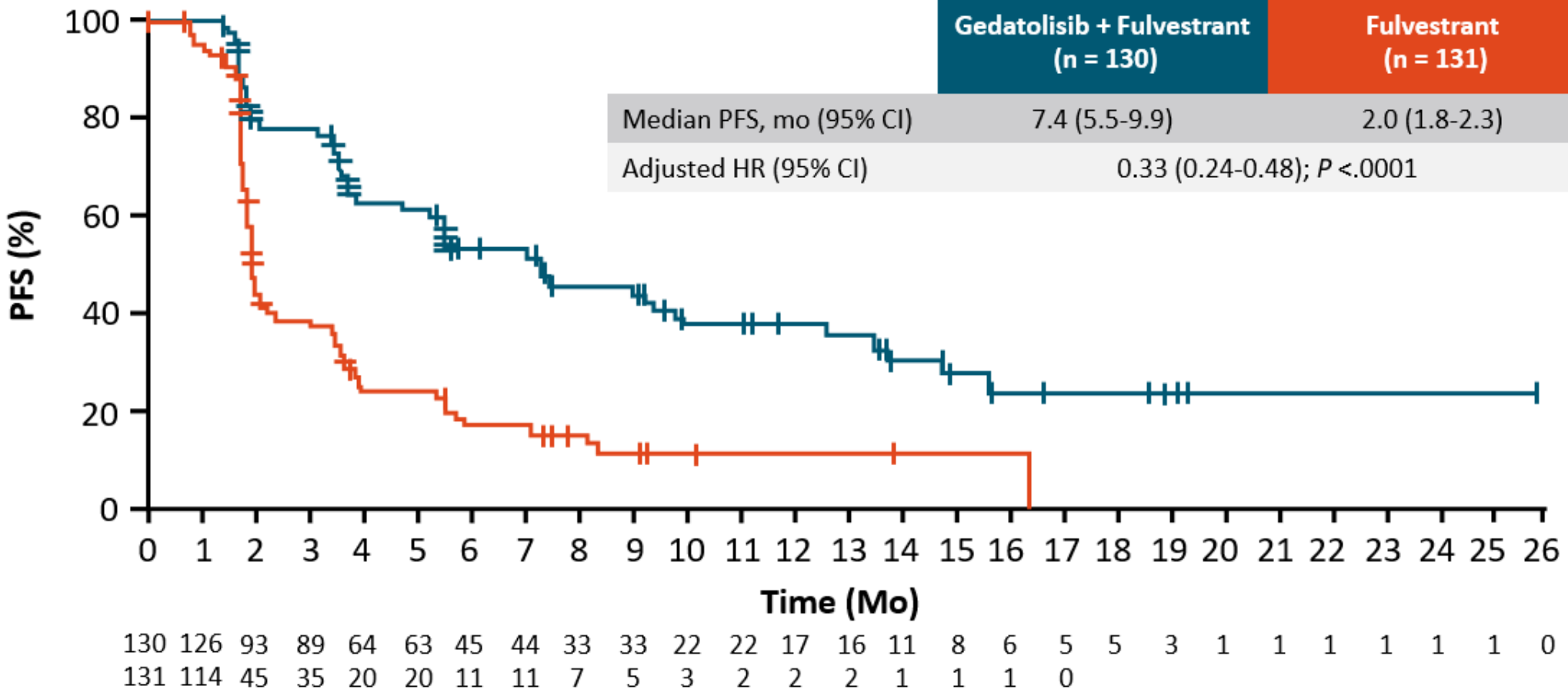
VIKTORIA-1: PFS With Gedatolisib + Fulvestrant vs Fulvestrant (Coprimary Endpoint)

	Gedatolisib + Fulvestrant (n = 130)	Fulvestrant (n = 131)
Median PFS, mo (95% CI)	7.4 (5.5-9.9)	2.0 (1.8-2.3)
Adjusted HR (95% CI)	0.33 (0.24-0.48); *P* <.0001	



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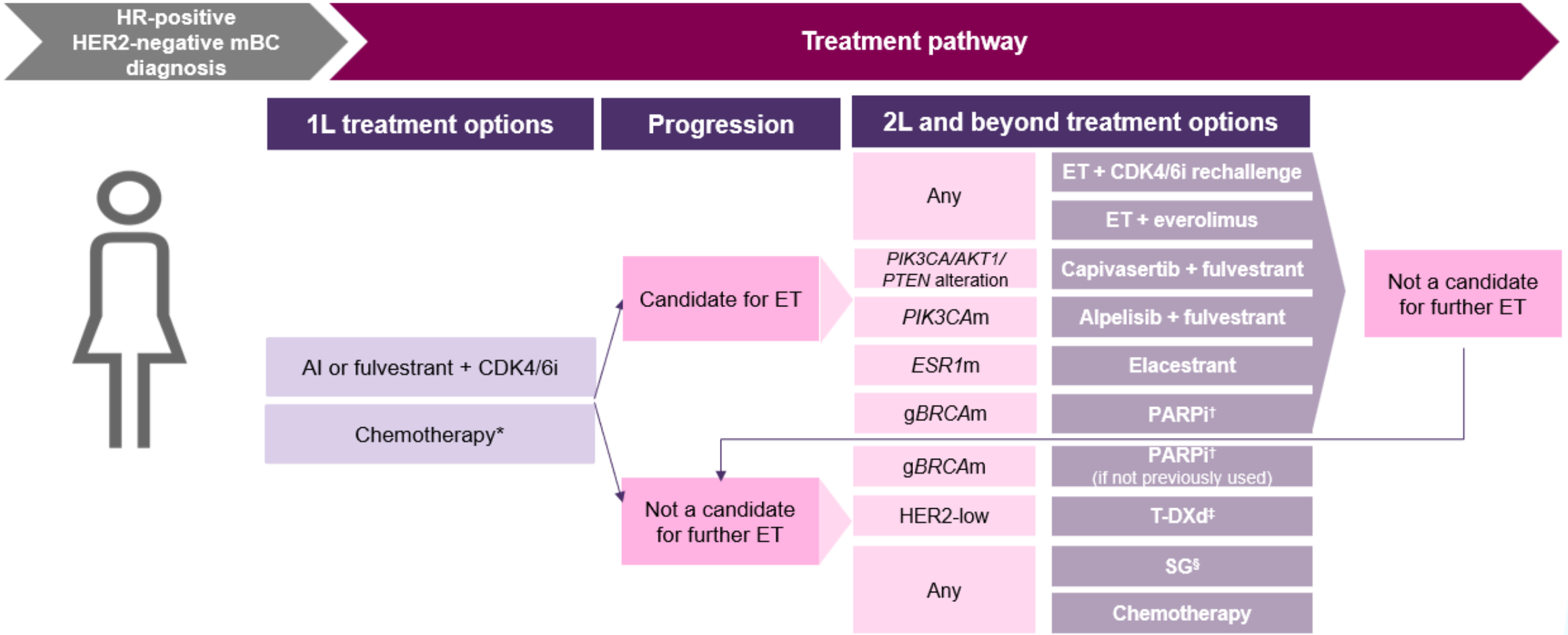
VIKTORIA-1: Investigators' Conclusions

- In phase III VIKTORIA-1 trial, combination of gedatolisib and fulvestrant ± palbociclib vs fulvestrant show statistically significant and clinically meaningful improvement in PFS in patients with HR+/HER2- aBC and *PIK3CA* wild-type status progressing on previous CDK4/6i therapy
  - mPFS in triplet vs fulvestrant: 9.3 vs 2.0 mo (HR: 0.24; 95% CI: 0.17-0.35; *P* <.0001)
  - mPFS doublet vs fulvestrant: 7.4 vs 2.0 mo (HR: 0.33; 95% CI: 0.24-0.48; *P* <.0001)
- Efficacy of gedatolisib-based therapy was similar across previous alternative specific CDK4/6i received
- TRAEs were mostly mild to moderate in severity (grade 1/2)
  - Incidence of hyperglycemia was low (9.2% in triplet arm and 11.5% in doublet arm), and diarrhea occurred in 16.9% and 12.3% of patients, respectively
  - Discontinuation of therapy due to AEs was uncommon, reported in only 2.3% of patients receiving the triplet and 3.1% receiving the doublet
- Investigators conclude that gedatolisib + fulvestrant ± palbociclib is a new potential SoC for patients with HR+/HER2- *PIK3CA* wild-type aBC following progression on/after a CDK4/6i

Hurvitz. ESMO 2025. Abstr LBA17.

Current SoC 1L treatments for HR-positive HER2-negative aBC include an AI or fulvestrant, combined with a CDK4/6 inhibitor, with multiple SoC (and non-SoC) options in 2L[1,2]



*If patient is at risk of imminent organ failure; †In gBRCAm patients only, following prior ET and if no risk of organ failure; ‡Post one line of chemotherapy, §Post two lines of chemotherapy

1L= first-line; 2L= second-line; 3L= third-line; AI=aromatase inhibitor; *AKT1=AKT serine/threonine kinase 1 (gene)*; (a)(m)BC=(advanced)(metastatic) breast cancer; g*BRCA*m= germline breast cancer gene mutated; ER=oestrogen receptor; *ESR1*m=oestrogen receptor alpha (gene) mutated; CDK=cyclin dependent kinase; chemo=chemotherapy; ET=endocrine therapy; HR+=hormone receptor-positive; HER2=human epidermal growth factor receptor 2; mono=monotherapy; mTOR=mammalian target of rapamycin; PD-L1=programmed death-ligand 1; PI3K=phospoinositide 3-kinase (protein); *PIK3CA*m=phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (gene) mutated; PR=progesterone receptor; *PTEN*=phosphatase and tensin homologue (gene); SG=Sacituzumab govitecan; SoC=standard of care.

1. Gennari A, et al. *Ann Oncol*. 2021;32:1475–1495; 2. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer v1.2024.

DESTINY-Breast06: Trastuzumab Deruxtecan vs CT in Previously Treated HR+/HER2-Low or HER2-Ultralow MBC

- Multicenter, open-label, randomized phase III trial

Stratified by: prior CDK4/6 inhibitor use (yes vs no); HER2 IHC 1+ vs 2+/ISH- vs 0; prior taxane in nonmetastatic setting (yes vs no)

Patients with HR+ metastatic breast cancer with PD on ≥2 previous ET ± targeted therapy (no prior CT) for MBC*; HER2 low (IHC 1+, or 2+/ISH-) or HER2 ultralow (IHC† >0 <1+) based on central IHC assessment using most recent evaluable IHC sample (N = 866)

1:1

T-DXd
5.4 mg/kg Q3W
(n = 436)

Physician's choice of CT
(capecitabine, paclitaxel, or *nab*-paclitaxel)
(n = 430)

Until PD or toxicity

*Also allowed: 1 prior line for MBC and PD ≤6 mo of starting 1L ET + CDK4/6 inhibitor or 1 prior line for MBC and recurrence ≤24 mo of starting adjuvant ET.
†HER2 IHC >0 defined by any IHC staining up to 10% of tumor cells.

- **Primary endpoint:** PFS (per BICR) in HER2-low population
- **Key secondary endpoint:** OS in HER2-low population, PFS (per BICR) and OS in ITT
- **Other secondary endpoints:** PFS (per INV) in HER2-low population, ORR and DoR (per BICR/INV) in HER2-low population and ITT, safety and tolerability, PROs

Curigliano. ASCO 2024. Abstr LBA1000. NCT04494425.

DESTINY-Breast06: Efficacy

HER2-Low Population	T-DXd (n = 359)	CT (n = 354)	HR (95% CI)	*P* Value
Median PFS by BICR, mo *Primary endpoint*	13.2	8.1	0.62 (0.51-0.74)	<.0001
12-mo OS rate,* %	87.6	81.7	0.83 (0.66-1.05)	.1181
HER2-ITT Population	**T-DXd (n = 436)**	**CT (n = 430)**	**HR (95% CI)**	***P* Value**
Median PFS by BICR, mo	13.2	8.1	0.63 (0.53-0.75)	<.0001
12-mo OS rate,† %	87.0	81.1	0.81 (0.65-1.00)	NR
HER2-Ultralow Population	**T-DXd (n = 76)**	**CT (n = 76)**	**HR (95% CI)**	***P* Value**
Median PFS by BICR, mo	13.2	8.3	0.78 (0.50-1.21)	NR
12-mo OS rate, %	84.0	78.7	0.75 (0.43-1.29)	NR

- T-DXd showed consistent PFS benefit across prespecified patient subgroups, regardless of age, HER2-low status, prior exposure to CDK4/6i or taxane, number of prior ET lines, endocrine resistance, or liver metastases

*20.1% of patients in the CT arm received T-DXd after CT discontinuation. †17.9% of patients in the CT arm received T-DXd after CT discontinuation.

Curigliano. ASCO 2024. Abstr LBA1000.

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1- La terapia hormonal de segunda línea sigue siendo el manejo del cáncer de mama con RH

2- La introducción de nuevas combinaciones y el desarrollo de agentes dirigidos , ofrece mayor SLP y una mejor calidad de vida

3- El abordaje personalizada maximiza los beneficios terapéuticos y minimiza toxicidades

4- Persisten desafíos relacionados con la aparición de resistencia y la selección optima

"No hay que temer a nada en la vida, sólo tratar de comprender."

Marie Curie

El conocimiento compartido hoy es la semilla de los avances del mañana

Muchas gracias